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THE CLINICAL SIGNIFICANCE OF THE Rh FACTOR WITH COMMENTS CONCERNING THE LABORATORY PROBLEMS*

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IN 1940, Landsteiner and Wiener [1] discovered the existence of a new blood group factor in man following the injection of rabbits with the blood of the *Macacus rhesus* monkey. The serum of the immunized rabbits clumped not only the blood cells of the Rhesus monkeys but also the blood of about 85 per cent of *human beings* irrespective of their blood groups, thus revealing the presence in man of a new blood factor designated as Rh, because it was first found in the Rhesus monkey.

Present knowledge of the Rh factor can be summarized as follows [2]: (*a*) it is an antigenic substance in human red blood cells similar in some respects to other previously discovered antigenic factors, the most important of which are those known as A, B, M and N; (*b*) it is inherited as a Mendelian dominant as are the others; (*c*) it occurs only in the red cells, resembling in this respect M and N, but differing from A and B, which occur in tissues and secretions of at least some persons; (*d*) the Rh agglutinogen occurs in about 85 per cent of white people, in about 92 per cent of negroes, in about 100 per cent of the Chinese [3] and in all *Macacus rhesus* monkeys; (*e*) there are *no normal* agglutinins against the Rh factor in man, again resembling the factors M and N, whereas such agglutinins are present normally against A and B (e.g., natural isoagglutinins a and b); (*f*) on the other hand, when blood containing the Rh factor (Rh +) is introduced into a person without it (Rh —), agglutinins may develop against it (called anti-Rh agglutinins); (*g*) however, no anti-M or N agglutinins ever develop if blood containing the M or N factors is injected into persons without these

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factors in their blood (i.e., M negative or N negative recipients). Therefore, from the above it can be seen that the Rh factor has iso-immunizing ability, whereas the M and N factors lack it. That is why the M and N factors have no significance with respect to hemolytic reactions in blood transfusions whereas the Rh factor is very important in this respect.

Hemolytic Reactions after Transfusions

Soon after the discovery of the Rh factor Wiener and Peters [4] studied the blood of patients who had hemolytic reactions after one or more previous uneventful transfusions of blood of the correct homologous group. The serum of these patients contained atypical isoagglutinins (anti-Rh agglutinins) which clumped the red blood cells of donors containing the Rh factor (Rh +). These same sera, therefore, behaved in a similar way to the sera of rabbits immunized with monkey blood (also Rh +). Therefore, it was concluded that the blood of these patients did not contain the Rh factor (as they were Rh negative), and, therefore, the presence of the atypical agglutinins (anti-Rh agglutinins) found in their serums was explained by assuming that Rh + blood was given to them during one or several of the transfusions which they had received previously. The fact that they did not possess the Rh factor in their own blood made it possible for the injected Rh positive blood to act as an antigen and, therefore, to stimulate the production of anti-Rh agglutinins. After the agglutinins had developed in these patients, it was then realized that Rh + blood from donors for transfusion purposes was not suitable for these patients even if the donors did belong to the identical blood group AB, A, B or O. Confirming this concept was the fact that whenever Wiener and Peters administered Rh + blood to these patients, they developed hemolytic reactions. Subsequent reports, by other authors, have confirmed these observations. That is, it has been found that patients showing hemolytic reactions after one or several previous uneventful transfusions of blood of the correct group AB, A, B or O were as a rule Rh — and that some of them had anti-Rh agglutinins in their blood. Therefore, in order to prevent further hemolytic reactions following transfusions, only Rh — blood donors could be used.

Pregnancy and Erythroblastosis

The same mechanism has been found to be responsible for reactions after first transfusions given to pregnant women. In such instances, however, the development of the anti-Rh agglutinin is explained by the presence of the Rh factor (Rh +) in the blood of the fetus to whom it was transmitted by the father as a Mendelian dominant and by the passage of this Rh factor through the placenta to the mother—who was thus immunized during pregnancy (i.e., the mother developed anti-Rh agglutinins). Bearing these facts in mind, Levine [5] suggested that erythroblastosis fetalis may be caused by a similar mechanism, and postulated that the production of anti-Rh agglutinins

in the mother is followed by placental passage of the agglutinins to the fetal blood with subsequent hemolysis of fetal blood and the clinical state of erythroblastosis fetalis. Since the mother's blood contains the anti-Rh agglutinins it reacts with Rh + blood cells of the fetus and destroys them. The correctness of this hypothesis is based upon at least four conditions:

1. The father must have the Rh factor as a Mendelian dominant factor (Rh +) in his blood in order to transmit it to the fetus.
2. The fetus must have the inherited Rh factor in his blood (Rh +).
3. The mother must lack the Rh factor (Rh —) in order to develop anti-Rh agglutinins in response to the passage of the Rh factor from the fetus through the placenta.
4. There must be a free exchange of antigenic substances and of antibodies through the placenta from the fetus to the mother and there must be a mechanism whereby Rh + fetal cells can escape into the Rh — maternal circulation. This mechanism probably is placental injury. The fulfillment of the fourth of these conditions can be taken for granted. The passage of protein substances from the fetus to the mother and of antibodies from the mother to the fetus has been previously satisfactorily demonstrated.

The only safe way to transfuse an Rh — person who has received previous transfusions, or an Rh — pregnant woman, or an infant with erythroblastosis, is to use known Rh — blood. An important problem is where such blood can be obtained, and it must be obtained from donors who are known to be Rh negative. For this purpose an Rh — donor pool should be established by determining the Rh negativity or positivity of a large group of people. The technic used for that purpose is described later in this paper.

The following four patients were observed in a period of six weeks in the Emory University Hospital, all presenting different types of Rh problems. The observance of this number in such a short time illustrates forcibly the necessity for careful consideration of the Rh problem in clinical medicine.

Case Reports

Case 1. Isoimmunization during Pregnancy and Its Rôle in Erythroblastosis Fetalis: This patient was a two day old, severely jaundiced, eight-pound, white, male infant who was delivered spontaneously at full term on March 8, 1943. The mother was a 28 year old multipara and had two children in perfect health, aged one and three years respectively. In her two previous pregnancies she had an uneventful prenatal, parturition, and puerperal course. Furthermore the prenatal course of this third pregnancy was also normal. Examination of the placenta at the time of delivery showed several small infarcts. Physical examination of the baby revealed a well developed, two day old, white male with a spleen that was palpable 4 cm. below the costal margin and the liver enlarged 2 cm. below the right costal margin. No enlarged lymph nodes were palpable. Blood examination showed: Red blood cells 2,350,000 per cu.mm.; hemoglobin 52 per cent; white blood cells 18,420 per cu.mm.; (neutrophiles 60, lymphocytes 39, and monocytes 1). The stained smear showed

marked variation in size, shape, and color of the red cells with many macrocytes and microcytes. In addition a large number of immature red blood cells were seen consisting chiefly of normoblasts. Based upon these essential criteria of severe jaundice, enlarged liver and spleen, severe anemia with the presence of large numbers of nucleated red cells, the diagnosis of erythroblastosis fetalis was considered to be established. Because of the marked anemia which was caused by excessive hemolysis of the fetal red cells, the infant was then given 50 c.c. of maternal blood, using 25 c.c. in each buttock intramuscularly. No improvement was noted in a 24-hour period and then 100 c.c. of the father's blood were given intravenously. A subsequent blood count revealed a red cell count of 2,100,000 per cu.mm., hemoglobin 42 per cent, and a considerable increase in the number of immature red cells in the blood. It was at this time that Rh determinations were made and these revealed the father to be Rh +, the mother Rh —, and the infant Rh +. Determination of the titer of anti-Rh agglutinins in the mother was then made and found to be 1 : 1024. All three members of this family were type O. Two subsequent transfusions of 100 c.c. each from Rh — Type O donors were entirely successful and the patient's red cells and hemoglobin rose to normal limits with a disappearance of immature red cells and gradual reduction in icterus, with decrease in size of the liver and spleen during a period of 10 days after delivery. This case illustrates the fairly typical findings in an infant with erythroblastosis fetalis, born of a multiparous mother—the immunizing antigen or Rh + fetal red cells entering the maternal circulation through a placental defect and producing isoantibodies in the Rh — maternal blood. These in turn, since they are soluble products, were passed back into the fetus in sufficient titer to cause severe hemolysis of the fetal red blood cells leading to erythroblastosis, jaundice, hepatomegaly, and splenomegaly. Also, this case illustrates why the mother's blood or the father's blood is contraindicated for transfusion purposes into erythroblastotic infants and why a donor list of Rh — donors should be available for such emergencies. It should again be emphasized that neither the father's nor mother's blood is satisfactory for transfusion into an erythroblastotic infant, although this is exactly the practice that is followed in well over 90 per cent of such cases simply because of availability of the blood. It is obvious that transfusion of the mother's blood simply confers upon the infant more anti-Rh agglutinins, or the transfusion of the father's blood confers more Rh + cells to be hemolyzed by the anti-Rh agglutinins that are already present.

Case 2. A Transfusion Accident Resulting from Anti-Rh Immunization during Pregnancy: This patient, who was a 25 year old primigravida, was delivered on April 24, 1943, in the Emory University Hospital of a full term, normal white, male infant. During the course of delivery the patient sustained a lateral rupture of the placenta 5 cm. from its margin which resulted in excessive hemorrhages during the remainder of parturition. Since the patient was Type O a male donor of the same group was obtained. When the crossmatch was set up at room temperature there was no evidence of agglutination. Therefore, a transfusion of 500 c.c. of blood was begun. After nearly 200 c.c. had been given, the patient developed a severe shaking chill, headache, elevated temperature, a rapid pulse rate, and severe pain in the flanks. Transfusion was discontinued. Adrenalin was administered and heat applied, and these symptoms subsided in the course of one to two hours. The crossmatch was then again set up and the blood was found to be wholly compatible. At that time, examination of the mother's blood revealed that she was Rh — and in addition showed a titer of 1:16 of anti-Rh agglutinins whereas the blood of the donor was Rh + and also that of the infant was Rh +. Following this the patient was given a transfusion of Rh — Type O citrated whole blood without any reaction whatever.

It is characteristic that this type of hemolytic transfusion accident occurs at the first transfusion of the pregnant woman or the woman who has re-

cently delivered. These accidents, of course, are of great significance to the obstetrician and gynecologist because of the relative frequency with which transfusion difficulties have always occurred in pregnant women in spite of the fact that patient and donor may be of the same blood group and the blood entirely compatible. It should be borne in mind that a pregnant woman may develop a rather substantial titer of anti-Rh agglutinins and at the same time the titer may not be sufficient or they may not gain access to the fetal circulation in such amounts as to produce marked hemolysis of fetal red cells and consequently the clinical picture of erythroblastosis fetalis. In this case, for example, there was no evidence of erythroblastosis in the newborn infant, yet the mother showed a titer of 1:16 of anti-Rh agglutinins, which, although not sufficient to destroy fetal red cells, was quite sufficient to give a marked transfusion reaction.

Case 3. Immunization after Multiple Blood Transfusions: This patient was a 58 year old white female admitted to the Emory University Hospital on April 6, 1943, with an established diagnosis of aplastic anemia. Her past history revealed nothing remarkable until one year prior to admission when she experienced her first evidence of gradual progressive weakness and fatigue. At that time a thorough physical examination was negative except for slightly reduced hemoglobin and red cells. Four months before admission, she noticed bruises on her lower extremities which were spontaneous purpuric spots. At that time she was hospitalized and her blood showed the following: Red blood cells 1,200,000 per cu.mm.; hemoglobin 30 per cent; white blood cells 2,600 per cu.mm., with a predominance of lymphocytes. During this hospital stay which was in North Carolina, the patient received six transfusions, one in February, four in March, and one during April. Careful questioning revealed that the first two transfusions were uneventful but that each succeeding one produced a more severe reaction, including a shaking chill, elevated temperature, rapid pulse, and pain in the flanks, and the last one produced, in addition, nausea and vomiting. On admission to the Emory Hospital she presented a marked pallor of the skin and mucous membranes with many diffuse and patchy ecchymotic areas over the entire body. Her red cell count was 2,000,000 per cu.mm.; hemoglobin 35 per cent, 5.7 gm.; white cells 1,350 per cu.mm. with 85 per cent lymphocytes; reticulocytes 0.1 per cent; and no blood platelets were seen on the stained smear. Because of the fact that she had been given multiple transfusions with reactions of increasing severity, the patient, who was a Type A, was tested for Rh factor. She was found to be Rh — and also to have a titer of anti-Rh agglutinins of 1:64. She was then transfused from our permanent Rh — donor list, the typing and crossmatching being carried out at room, incubator, and refrigerator temperatures. Five hundred c.c. of blood were then given without reaction. It is of interest that in this particular transfusion this blood was administered by way of the sternal marrow since the patient's veins were not in suitable condition for the administration of blood. After this one other Rh — transfusion was given but no further blood was administered after this time since we felt that her prognosis was hopeless. This patient succumbed to her disease, aplastic anemia, on the twenty-sixth hospital day, the red cell count having reached the low level of 800,000 per cu.mm. at that time. This case demonstrates the production of anti-Rh agglutinins in an Rh — patient by means of multiple transfusions of Rh + donors of homologous blood groups. It serves to illustrate a principle which must be emphasized, that is, Rh determinations should be done on all medical and surgical cases who are to receive or who have had more than one transfusion.

Case 4. The Development of Anti-Rh Agglutinins as a Surgical Problem: This patient was a 40 year old white female who was admitted to the Emory University Hospital on March 14, 1943, with a history of progressive weakness, frontal headaches, malaise, slow loss of weight, and pain in the left upper abdominal quadrant. Examination of this patient revealed a marked pallor of the skin and mucous membranes, a slight brownish skin discoloration, a visible superficial network of veins over the chest and abdominal wall, numerous ecchymotic areas over the trunk and lower extremities, and a marked enlargement of the spleen. The patient had known of the presence of this large hard mass in her upper left abdomen for a period of six years prior to admission. A tentative diagnosis of Banti's syndrome was made and after this tests for liver function were carried out using the (bromsulfthalein) dye test, hippuric acid synthesis test, and the cephalin cholesterol test. Liver function was found to be normal, and the liver was not enlarged. Examination of the blood showed a hemoglobin of 40 per cent; red cells 2,500,000 per cu.mm.; and a leukopenia of 2,200 cells per cu.mm., with an essentially normal differential count. Based upon the presence of an enlarged spleen of presumably six years' duration, the rather marked anemia, the presence of leukopenia, and a well-developed collateral circulation over the trunk, a diagnosis of Banti's syndrome was made. It was then decided to remove the spleen, and because of her low hemoglobin and red cells it was considered necessary to prepare her for splenectomy by two or more blood transfusions.

The patient was the mother of three, living, healthy children, the last child being eight months old, and since she was only eight months postpartum it was decided to test her for Rh factor. She was found to be Rh — and in addition to this, much to our astonishment, she showed a titer of anti-Rh agglutinins of 1:1024. It was felt, of course, that it would be unwise to transfuse her with Rh + blood. Whereupon she was transfused with two Rh — transfusions without reaction and after this splenectomy was successfully performed, from which she made an uneventful recovery. At this time the blood findings of this patient are entirely normal, the leukocyte count being 10,000 cells per cu.mm. The spleen was characteristic of Banti's syndrome, that is to say, it was an organ characterized by excessive fibrosis. This case presents an example of the value of prophylactic measures to avoid transfusion reactions. An astonishing feature of this patient was the fact that she carried such a high titer of anti-Rh agglutinins which presumably resulted from her last pregnancy which occurred eight months before. We can only speculate as to what might have happened to this patient if she had been given a transfusion of Rh + blood.

Technic of Preparation of Reagents and the Details of the Test for the Rh Factor

Since the advent of the Rh problem in clinical medicine and general recognition of its importance, a justifiable demand has been made on pathologists and other laboratory personnel to aid in the solution of these problems as they arise in clinical practice. Thus, there must be available materials and methods for determining Rh negativity and positivity; the presence and titer of anti-Rh agglutinins in patients, and methods for pretransfusion crossmatching of blood that will detect incompatibilities not only of major blood groups but of Rh factor as well. The following is an attempt to summarize the procedures involved in these problems.

Before one can begin to determine the Rh positivity and negativity of a given number of donors, there must be available a suitable quantity of a

known *serum* containing the specific anti-Rh agglutinins. Such serum may be obtained from three sources as follows:

1. By Purchase: Small amounts of Rh negative serum containing anti-Rh agglutinins can be obtained from the Certified Blood Donor Service, 146 Hillside Avenue, Jamaica, New York at cost of approximately $5.00 per c.c. Then, by using the following technic with the above anti-Rh serum, one can obtain a small list of known Rh negative and positive donors:

"Prepare a *fresh* saline suspension (2 per cent) of the red blood cells to be tested. Before proceeding with the test examine a drop of this suspension microscopically to make sure that there is not peculiar agglutination or hemolysis of red blood cells. Then using a culture tube of $3 \times 3\frac{3}{8}$", place on the bottom of the tube one good sized drop of the fresh saline suspension prepared and tested as above. This drop should be approximately .05 c.c. Carefully place into the same tube 1 large drop of the known anti-Rh serum. This drop should be as close as possible in size to that of the cell suspension already in the bottom of the tube. If smaller amounts of serum and cell suspension are used the result will be difficult to read. If larger amounts are used, there will be an unnecessary waste of anti-Rh serum. Then shake very lightly. Place in a water bath at 37° C., for 1 to 1½ hours. Centrifuge at 500 RPM for one minute and observe sedimented blood. Resuspend *gently —very gently.* Read the result at the bottom of the tube macroscopically for clumping. Where clumping is evident, the result is Rh positive (very rarely a minor degree of clumping is seen due to anti-M isoagglutinins). Those that seem to be negative macroscopically are then examined under the microscope (low power). Those that show no clumping are now definitely Rh negative. A small drop may be easily removed from the test tube by means of a small glass rod or a platinum loop. This drop may be placed on a microscope slide and examined microscopically. Whenever doubt arises, check again the original suspension of unknown red blood cells, and start with a definite unagglutinated suspension of red cells. This rules out pseudo and cold or autoagglutinins."

2. Obtaining Large Amounts of Serum from Erythroblastotic Mothers: The most reliable source of serum is from women who have been immunized during pregnancy or who have given birth to infants with clinical erythroblastosis fetalis. The Rh factor in the fetus is responsible for the iso-immunization in the great majority of cases, but other blood factors may also immunize. In order to determine whether the mother's serum contains any anti-Rh agglutinins (since in at least 50 per cent of the cases there are no demonstrable antibodies of the Rh type [6]), the following is thought to be a satisfactory working procedure:

Remove about 10 c.c. of blood from the patient and recover the serum. First remove the isoagglutinins a and b present in the serum of group A, B and O patients. This is done to prevent the interaction between the

"natural" isoagglutinins of the serum being tested and the agglutinogens in the red cells containing agglutinogen A of Group A red cells and agglutinogen B of Groups B red cells. According to Witebsky and his associates,[7] the addition of the recently isolated group-specific substances A and B leads to a marked reduction or elimination of the isoagglutinins anti-A (*a*) and anti-B (*b*) present in the specific blood groups or present together in the serum of so-called universal blood of Group O.* For this purpose, it has been found that the addition of approximately 1–2 c.c. of the AB containing solution (prepared by Eli Lilly and available for experimental purposes only) to 5 c.c. of the patient's serum is sufficient to neutralize the natural iso-agglutinins a and b.

The serum must then be tested for neutralization of these isoagglutinins and in order to do this the following titration agglutination setup is thought to be adequate. Serial dilutions of serum in decreasing amount (volume 0.2 c.c.) are mixed with 0.2 c.c. each of a 1 per cent suspension of human red blood cells belonging to group A and group B respectively. After standing for 30 minutes at room temperature, the tubes are centrifuged for about one minute. The resulting agglutination is recorded as in the following table:

Tube No.	Dilution	Part 1 Before Addition of Group Spec. Sub.		Part 2 After Addition of Group Spec. Sub.	
		Group A Cells	Group B Cells	A Cells	B Cells
1	Undiluted	++++	++++	++	+
2	1 : 2	++++	++++	+	−
3	1 : 4	++++	++++	−	−
4	1 : 8	++++	+++	−	−
5	1 : 16	+++	+++	−	−
6	1 : 32	++	++	−	−
7	1 : 64	++	+	−	−
8	1 : 128	+	+	−	−
9	1 : 256	+	−	−	−
10	1 : 512	−	−	−	−
11	1 : 1024	−	−	−	−
12	Saline control	−	−	−	−

Note: If there is still insufficient neutralization, 1 or 2 c.c. more of the Witebsky AB solution can be added.

Having determined that complete neutralization of the natural agglutinins has occurred, it is then necessary to determine the specificity of the anti-Rh

* Convenient sources for the isolation of group specific substance A are commercial pepsin, mucin and peptone. The addition of 25 mg. of specific substance A to 500 c.c. group O blood reduces the titer of the isoagglutinin anti-A considerably or at times even completely. The B substance was finally isolated from the gastric juice of human beings belonging to group B. A 1:1,000 stock solution of group specific substances is prepared, 25 c.c. of stock solution of A substance and 10 c.c. of stock solution of B substance are kept in vaccine bottles under sterile conditions and added to 500 c.c. of citrated blood five minutes previous to administration of blood, i.e., if one is to use universal donor blood safely (Group O).

serum obtained from the patient by determining not only the presence of the anti-Rh agglutinins but their strength or titer as well. This should be done according to the following table, *using known Rh + Cells, Group O,* since no agglutinogens are present in that group.

Titer					
1 : 2	Normal saline (large drop)	+			
	large drop of anti-Rh serum	− −	very gently shake	—	add large drop of 0.2% Red Blood Cell saline suspension
1 : 4	Large drop normal saline	+			
	large drop of no. 1 mixture	− − −	"	—	"
1 : 8	Large drop normal saline	+			
	large drop no. 2 mixture	− − −	"	—	"
1 : 16	Large drop normal saline	+			
	large drop no. 3 mixture	− − −	"	—	"
1 : 32	Large drop normal saline	+			
	large drop no. 4 mixture	− − −	"	—	"
1 : 64	Large drop normal saline	+			
	large drop no. 5 mixture	− − −	"	—	"
1 : 128	Large drop normal saline	+			
	large drop no. 6 mixture	− − −	"	—	"
1 : 256	Large drop normal saline	+			
	large drop no. 7 mixture	− − −	"	—	"
1 : 512	Large drop normal saline	+			
	large drop no. 8 mixture	− − −	"	—	"
1 : 1024	Large drop normal saline	+			
	large drop no. 9 mixture	− − −	"	—	"
1 : 2048	Large drop normal saline	+			
	large drop no. 10 mixture	− − −	"	—	" , remove and discard one drop.

Saline control—Large drop of normal saline + large drop of 0.2% RBC saline suspension.

Shake all tubes *very gently*—place in water bath for 1 to 1½ hours at 37° C. Centrifuge for one minute at 500 RPM and observe sedimented blood. Resuspend *gently, very gently* (count the number of shakes required to resuspend the tube number 11 and use the same number of shakes to resuspend the others). Read the results under microscope (low power). The highest dilution at which agglutination occurs is the titer of the anti-Rh serum. It is preferable to use a serum with a titer of 1:128 or above; therefore, for economical purposes it may be desirable to dilute strong titer solutions to this strength, but on the other hand, this may not be wise since the anti-Rh factor is lost rapidly and usually lasts no longer than three months.

The preservation of anti-Rh serum sometimes is rather difficult. It usually does not keep well in fluid state, since there is a gradual loss of potency, and should be kept either frozen or dried if the facilities are present. Since desiccation facilities are usually not available, there has been the constant problem of replenishing the laboratory supply of potent serum. This can be done only by constant lookout for new cases of erythroblastosis and attempts to obtain suitable serum from the mothers. When a large obstetrical service is available, this can be done, but even so there is the constant problem of being uncertain as to the titer of any serum in current use, and frequent titrations against known Rh + cells must be carried out. At the present time we are testing serum that was air-dried, using one drop on a cover glass, and after two months the potency seems unimpaired. If such air-dried

serum proves satisfactory after passage of sufficient time, this would promise a solution of this problem.

After having determined that the serum contains a sufficiently high titer of anti-Rh agglutinins, the patient can be bled for a larger amount such as 100 to 200 c.c. for stock purposes. The agglutinins in the fluid serum should remain potent for about three months, although this is variable. The serum, of course, should be used as early as possible to establish a large pool of Rh — donors, using the technic as outlined previously. Anti-Rh serum can also be obtained from Rh — patients who have developed the antibodies from repeated transfusions of Rh + blood, but that from erythroblastotic mothers appears to be more satisfactory because of higher titers.

Anti-Rh serum may also be produced in laboratory animals by repeated injections of washed cells from the *Macacus rhesus* monkey, but at this time such sera are not reliable because of antigenic non-specificity.

The Modified Compatibility Test

In situations in which Rh — donors are not available and an Rh problem may be suspected, a modified type of cross matching, as recommended by Levine, should be done. This is known as the modified compatibility test and is carried out as follows:

An equal mixture of the patient's serum and prospective donor's cells is incubated in a small tube in a water bath for 15 to 30 minutes at 37° C. This mixture is then centrifuged at 500 RPM for one minute and the sediment resuspended is examined microscopically for the presence or absence of agglutination. In pregnancies of all types, for repeated transfusions, and in erythroblastotic infants, this Levine compatibility test should be done routinely.

Summary

1. A summary of existing knowledge concerning the Rh factor is presented.

2. Four cases illustrating variable Rh problems are presented.

3. Methods for obtaining and preparing anti-Rh serum are described in detail.

4. The importance of having donors ready and classified for the Rh factor is obvious; in fact, many workers in this field use Rh negative donors routinely for postpartum patients and patients having transfusion reactions of any kind unless there is time to study the case thoroughly and the Rh factor as a source of danger can be excluded.

5. Sera for testing for the Rh factor can be obtained (1) by purchase, (2) from patients who have had transfusion reactions caused by the Rh factor, (3) and from the mothers of erythroblastotic infants.

6. The agglutination reactions with anti-Rh sera, even those of high titer, are much weaker than those of ordinary blood group sera and may not show up at all by the ordinary slide technic.

7. The modified compatibility test should be used in all instances in which the Rh disturbances may be suspected.

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METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT. VIII. THE CHEMICAL COMPOSITION OF THE LIVER, ESPECIALLY IN PATIENTS WITH GASTROINTESTINAL CANCER*

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Introduction

Previous studies from this hospital have demonstrated that patients with gastrointestinal cancer frequently have several abnormalities of hepatic function.[1, 2] The existence of these disorders appears to be due to the presence of the neoplasm, for when it is removed the functional capacity of the liver improves.[2] The occurrence of hepatic insufficiency in these patients seldom has been found to be associated with those morphological alterations of the liver [3] commonly observed in patients who suffer from chronic alcoholism or cirrhosis.[4]

The possibility existed that even though the livers of patients with gastrointestinal tract cancer were morphologically intact, their chemical compositions might be abnormal. If this were the case it might be of clinical significance, since it would provide a possible explanation for the hepatic insufficiency shown by these patients, and would suggest an effective method for the treatment of this insufficiency. The last possibility is based upon the fact that the administration of certain dietary constituents to experimental animals with livers which contain abnormal amounts of fat and glycogen has been followed by a return of those organs to a normal chemical state and increased functional capacity.[5, 6]

The chemical composition of the livers of patients with cancer of the gastrointestinal tract has been studied and the effects of the administration of dietary factors observed. The results of these studies form the subject of this and the subsequent communication.

Material

Liver biopsies were obtained from one test and two control groups of patients. The test group consisted of 18 patients with gastrointestinal cancer. Of these, one had carcinoma of the terminal esophagus, 15 of the

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stomach, and two of the colon. Three patients had extension of the tumor to the liver.

The first control group comprised four patients: one with carcinoma of the head of the pancreas, one with toxic hepatitis, and two with chronic cholecystitis with impacted calculi in the common bile duct. This group was studied because their disorders are commonly associated with marked hepatic insufficiency and morphologic damage.[5, 6]

The second control group consisted of four patients who were operated upon for non-neoplastic lesions of the gastrointestinal tract. One had gastritis, two gastric ulcer, and one multiple duodenal ulcers. None suffered from pyloric stenosis. Patients with the disorders included in this group do not show any significant degree of hepatic dysfunction.

In all the diagnoses were confirmed by microscopic examination of the biopsied lesions.

Methods

A. Clinical: All of the 26 patients studied were hospitalized for from three to eight days before they were operated upon. They were given daily at least 2500 ml. fluid and a diet of from 2,000 to 3,000 calories. The ratio of carbohydrate: fat: protein in their diet was 5 : 1 : 1. Only clear fluids were given during the evening meal on the day before operation, and nothing thereafter. None received glucose or saline preoperatively.

Spinal anesthesia was used in all instances. The liver biopsies for chemical and microscopic study were obtained as soon as the peritoneal cavity was exposed. Specimens which weighed from 0.8 to 1.5 gm. were removed from the liver edge. Bleeding was controlled easily by the approximation of the cut surfaces by silk mattress sutures. As soon as the tissue was excised the fibrous capsule was removed and the remaining tissue was given to a laboratory assistant in the operating room. This was rapidly blotted and about 0.3 gm. placed in warm 30 per cent KOH for the glycogen determination. About 0.5 gm. was placed in a tared weighing bottle, weighed, and used for the determination of nitrogen and lipid. A small portion was fixed in formalin for histological study.

B. Chemical: 1. The glycogen was determined by the method of Good, Kraemer and Somogyi[7] as modified by Nutter.[8] The sugar content in aliquots of the hydrolysate was measured by the Shaffer and Somogyi technic.[9]

2. The protein and non-protein nitrogen fractions of the liver tissue were determined in fine aqueous suspensions. These were prepared by grinding about 300 mg. of the tissue with 10 ml. of water in an all glass homogenizer. The separation of the "protein" * and non-protein nitrogen fractions of this suspension was effected by the method of Robinson, Price, and Hogden.[10]

* It must be emphasized that the hepatic albumin and globulin fractions as presented in this study represent only those proteins which can be separated by precipitation with 22 per cent Na_2SO_4 at 37° C. This does not imply, therefore, that these protein fractions exist in the liver nor are they identical with serum albumin or globulin.

3. The liver total lipid was determined by the technic of Van Slyke et al.[11]

4. The protein concentration in the serum was ascertained by the method of Weech et al.[12]

Results

The results of this study will be presented in three sections: Those which deal with the hepatic content of glycogen, of fat, and of protein.

A. Glycogen: The glycogen content of normal human livers probably is not known, for most analyses have been made on postmortem material. The pre-agonal state probably alters the chemical composition of liver tissue,[13] and postmortem autolysis of hepatic glycogen occurs very soon after death. The postmortem glycogen levels in the liver tissue of normal individuals who died suddenly are reported to range from 2 to 8 gm. per cent.[14, 15] The values during life probably are somewhat higher. Although some measurements of glycogen have been made on liver tissue obtained at laparotomy,[16, 17] the patients were subject to disorders associated with hepatic dysfunction.

In the 18 patients studied with gastrointestinal cancer the glycogen content ranged from 1.0 to 8.3 gm., and averaged 2.91 gm. per cent. In the first control group, that of patients with hepatic dysfunction due to toxic hepatitis or biliary tract obstruction, the liver glycogen ranged from 1.3 to 5.1 gm. and averaged 2.62 gm. per cent. These values are probably abnormally low and are in good agreement with those reported by Goldschmidt et al.[18] for patients with liver damage. The four patients with benign lesions of the alimentary tract who form the second control group were found to have from 1.3 to 3.6 gm. of hepatic glycogen with an average of 2.28 gm. per cent. These patients were not found to have any hepatic dysfunction, nor were their livers morphologically abnormal. It appears either that the average value of 2.28 gm. per cent hepatic glycogen found in the patients with benign lesions is the amount present in the normal human liver, or that benign gastrointestinal disease is associated with abnormally low concentrations.

It is possible that the usual 10 hour preoperative fast decreased the glycogen stores in the livers of all the patients studied. Probably more revealing and reliable information could be obtained by the measurement of hepatic glycogen after the patients had received preoperatively large amounts of glucose. By these measurements an index of the ability of these patients to fabricate and store glycogen in the liver could be determined. Data of this nature now have been obtained and are included in the subsequent communication.[19]

B. Fat: The normal fat content of human livers is not definitely known. Values of from 2.4 to 8.5 gm. per cent lipid have been found [13] in the livers of normal individuals who were autopsied within several hours after death as a result of trauma. Although the hepatic content of fat probably does not change significantly within so short a time after exitus, it is admitted [13]

that the pre-agonal state may alter the content of fat as well as that of other constituents.

The average concentration of total lipid in the livers of the 18 patients with gastrointestinal cancer was 17.43 gm. per cent, and the range from 5.3 to 35.0 gm. per cent. Of the 18 values, 16 were higher than the highest "normal" value of 8.5 gm. per cent.[18] Thus, the livers of patients with gastrointestinal cancer frequently are infiltrated with fat, even though microscopic examination of the liver tissue fails to suggest that abnormality (when prepared by routine methods not specifically designed to demonstrate fat).

The lipid contents of the livers of patients with gastrointestinal cancer were as great as those of the patients in the first control group, those with carcinoma of the head of the pancreas, toxic hepatitis, or impacted calculus in the common bile duct. The values ranged from 11.5 to 26.6 gm. and averaged 17.47 gm. per cent.

The average fat content of the livers of four patients with benign gastrointestinal lesions, the second control group, was 11.82 gm. per cent, and ranged from 6.2 to 17.0 gm. per cent. Although these values are significantly lower than those of the other two groups of patients studied, they still are higher than those reported for normal livers procured at autopsy. These observations would suggest, that either the fat content of the "normal" liver decreases soon after death, or that the lipid content in the livers of patients with benign gastrointestinal lesions is somewhat increased over normal.

TABLE I

The Chemical Composition of Livers of Patients with Cancer of the Gastrointestinal Tract

Patient	Histologic Appearance of the Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent	Total Protein, gm. per cent	"Albumin," gm. per cent	"Globulin," gm. per cent	Serum Protein, gm. per cent
S. B.	Normal	1.3	12.5				
F. B.	Normal	3.6	22.0				
A. B.	Moderate fatty infiltration	1.9	24.0	14.7	3.9	10.8	6.6
H. D.	Normal	1.9	15.9	17.6	6.7	10.9	7.3
P. F.	Normal	1.0	14.8	17.2	5.1	12.1	7.2
T. G.	Normal	1.45	12.1	15.9	5.8	10.1	6.8
S. H.	Normal	1.8	5.3				
A. H.	Normal	2.2	13.0				
W. J.	Normal	2.7	8.55	15.8	5.5	10.3	5.7
M. P.	Normal	1.4	27.1	16.0	8.05	7.97	5.7
L. R.	Normal	4.0	9.5	17.95	4.6	13.35	7.1
L. S.	Normal	2.0	6.9	16.2	5.8	10.4	4.2
J. S.	Normal	5.8	24.1				
J. T.	Normal	8.3	14.8	17.8	3.2	14.6	6.7
J. T.	Moderate fatty infiltration	2.4	29.0				
V. T.	Normal	1.3	22.4	12.9	4.4	8.5	7.4
S. W.	Normal	2.1	35.0	16.8	4.3	12.5	4.6
E. Y.	Normal	7.3	16.9	15.2	4.1	11.1	6.2
Average.....		2.91	17.43	16.17	5.10	11.05	

TABLE II

The Chemical Composition of Livers of Patients with Considerable Hepatic Dysfunction

Patient	Disease	Histologic Appearance of the Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent	Total Protein, gm. per cent	"Albumin," gm. per cent	"Globulin," gm. per cent	Serum Protein, gm. per cent
W. K.	Impacted calculus in common bile duct	Moderate fatty infiltration	2.5	26.6				
J. R.	Impacted calculus in common bile duct	Normal	1.3	13.3				
B. R.	Toxic hepatitis	Chronic hepatitis	1.6	18.5	14.9	4.9	10.0	5.2
B. L.	Carcinoma of head of pancreas	Chronic hepatitis, peribiliary	5.1	11.5	12.3	5.0	7.3	7.4
Average			2.62	17.47				

TABLE III

The Chemical Composition of Livers of Patients with Benign Gastrointestinal Lesions

Patient	Disease	Histologic Appearance of the Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent	Total Protein, gm. per cent	"Albumin," gm. per cent	"Globulin," gm. per cent	Serum Protein, gm. per cent
T. B.	Duodenal ulcers	Normal	1.3	14.4	11.4	4.7	6.7	6.5
H. K.	Gastric ulcer	Normal	3.6	9.7	14.6	4.6	10.0	5.8
R. G.	Gastric ulcer	Normal	2.8	17.0	15.8	4.4	11.4	6.3
G. F.	Gastritis	Normal	1.4	6.2	16.6	3.9	12.7	5.9
Average			2.28	11.82	14.6	4.40	10.20	

An inverse relationship previously has been noted between the concentrations of fat and of glycogen in the livers of animals,[20] i.e., a high lipid content often is associated with depleted stores of glycogen. Although the existence of this relationship has been noted in most of the individuals included in the present study, several instances were found in which high values of glycogen were associated with abnormally high concentrations of hepatic lipid (table 1).

C. Protein: In previous studies from this hospital, 58 per cent of patients with gastrointestinal cancer have been found to be hypoproteinemic.[2] Moreover, when these individuals were subjected to surgical manipulation, with few exceptions their serum protein levels fell, often to exceedingly low values.[21] In most instances, the hypoproteinemia was due principally to a decrease of the albumin fraction.

It has been noted that the livers of fasted animals are depleted of proteins with great rapidity,[22] and that when animals are maintained on high protein diets all the protein fractions of their livers increase.[23] These observations,

therefore, suggest that the liver may store proteins, and that those stores might be abnormally reduced in the hypoproteinemic patients with gastrointestinal cancer. The concentrations of proteins in the normal human liver are not known and so not available for purposes of comparison. One may hazard, perhaps, a comparison of the values obtained with those of animal liver tissue. The total protein in the liver of the rat has been found to average 15.5 gm., the "albumin" 2.1 gm., and the "globulin" 13.4 gm. per cent [24]; in the dog liver the average total protein content has been found to be 17.5 gm. per cent.[25]

Of the 18 patients with gastrointestinal cancer the total hepatic protein was measured in 12. The levels ranged from 12.9 to 17.95 and averaged 16.17 gm. per cent. The "albumin" contents averaged 5.10 gm. and varied from 3.2 to 8.05 gm. per cent, and the "globulin" averaged 11.0 and ranged from 8.5 to 14.6 gm. per cent. No apparent correlation was found between the concentrations of protein in the serum and in the livers of the patients studied.

The two control groups gave similar findings. The total protein contents of the livers of two patients with marked hepatic dysfunction were 12.3 and 14.9 gm. per cent; the "albumin" contents 7.3 and 10.05 gm. per cent. The total protein in the livers of four patients with benign gastrointestinal lesions ranged from 11.4 to 16.6 gm. and averaged 14.6 gm. per cent; that of "albumin" ranged from 3.9 to 4.7 gm. and averaged 4.40 gm. per cent; and that of "globulin" varied from 6.7 to 12.7 gm. and averaged 10.20 gm. per cent.

It is interesting to note that the liver apparently does not contain large stores of "albumin." Assuming an average liver weight of 1,500 gm., the average concentration of 4.1 gm. per cent obtained for hepatic "albumin" would amount only to 61.5 gm. of protein, or about one-quarter that of the normal circulating serum albumin. Thus, if the "albumins" of the liver are similar to those of the serum, or are converted readily into that fraction, the store they constitute for serum albumin replacement is a small one.

Discussion

The chemical composition of the liver has been demonstrated to determine the degree of susceptibility or resistance of the organ to various hepatotoxins. For example, there is general agreement that a high concentration of hepatic lipid is pathologic,[18] and that an adequate quantity of hepatic glycogen is protective,[16] but only in the absence of an abnormal content of liver fat.[17] Furthermore, it has been claimed that the administration of high protein diets to animals results in an increased protein content of the liver and affords protection of the organ against several otherwise toxic factors.[26]

Hence, the observation that the livers of patients with gastrointestinal cancer contain abnormally large amounts of fat and probably small amounts of glycogen, becomes of considerable interest. These patients frequently

receive large amounts of narcotics and barbiturates, and undergo considerable surgical manipulation and prolonged anesthesia. These procedures induce, even in the normal liver, a certain amount of transitory insufficiency.[27, 28] It could be expected, then, that patients with gastrointestinal cancer, whose livers are particularly susceptible to damage because of their altered chemical constitution, often would develop postoperatively a considerable degree of hepatic dysfunction.

The mechanisms by which glycogen exerts its protective effect against hepatic damage thus far is not known. However, since the normal metabolism of lipid depends upon the catabolism of carbohydrate, an adequate store of carbohydrate (glycogen) apparently is necessary to insure against an abnormal utilization of fat [29] and its consequent deposition in the liver.[30] Emphasis has been given to the fact that it is not the mere *presence* of glycogen in the liver but rather its *metabolism* which offers protection to the organ against certain toxic compounds.[17, 31]

Many compounds injurious to the liver normally are detoxified by conjugation with glucuronic acid. There now is reason to believe that the synthesis of that acid may depend upon an adequate store of glycogen.[32] It is interesting to note, in this connection, that 55 per cent of patients with gastrointestinal cancer [2] excreted abnormally small amounts of urinary glucuronates.

The mechanisms by which a high content of lipid contributes to development of liver damage probably are better understood. The abnormal deposition of fat in the liver has been shown to compress the sinusoids and consequently induce ischemia in certain portions of the organ.[33] Furthermore, lipid is deposited in the organ without water [34] (in contrast to the deposition of glycogen [35]), so that the available hepatic water must be distributed through a larger tissue volume; the fluid content of the cells consequently may be reduced, and the solution of essential water-soluble constituents decreased. Finally, the increased lipid content of the organ possibly favors the solution and retention in the tissue of many lipid soluble toxins.[18]

At this time no conclusions can be drawn from the values of the hepatic proteins because of a lack of adequate control material. Had a direct correlation been found between the concentrations of protein in the serum and in the livers of the patients studied, then a reasonable explanation for the hypoproteinemia noted so frequently in these individuals might have been a depletion of the hepatic "protein stores." The data obtained could not provide this explanation. The comparatively small amounts of "albumin" found in the livers of even those individuals who had normal serum protein levels, suggest that the liver does not constitute a ready store for serum albumin replacement.

The observation that the livers of patients with gastrointestinal cancer contain abnormally large amounts of fat and probably small amounts of

glycogen, suggests a means whereby the impaired hepatic functions of these individuals might be restored to normal. Recent investigations have shown that the administration of certain dietary constituents to experimental animals with livers depleted of glycogen or infiltrated with fat was able to correct their abnormal hepatic chemical composition and ability to withstand the damaging effects of hepatotoxins.[5, 6] Hence, if the hepatic dysfunction in the patient with gastrointestinal cancer was due to the fact that his liver was more susceptible to hepatotoxins because of its abnormal chemical constitution, then the correction of the altered constitution of his liver and its consequent susceptibility to continual damage, might be followed in time by a restoration to a normal functional capacity. Accordingly, attempts have been made to increase the glycogen content and decrease the fatty infiltration in the livers of these patients by the administration of dietary constituents. The results of that study are presented in the subsequent communication.[19]

Summary

1. A high incidence of fatty infiltration and probable glycogen depletion of the liver has been found in patients with gastrointestinal cancer.

2. The possibility is presented that these abnormalities of hepatic chemical constitution make patients with gastrointestinal cancer particularly serious surgical risks.

3. No relationship could be found between the concentration of protein in the serum and in the livers of patients with gastrointestinal cancer.

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METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT. IX. EFFECTS OF DIETARY CONSTITUENTS UPON THE CHEMICAL COMPOSITION OF THE LIVER, ESPECIALLY IN PATIENTS WITH GASTROINTESTINAL CANCER *

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INTRODUCTION

IN a previous investigation the livers of patients with gastrointestinal cancer were found to have abnormally high concentrations of fat and probably low concentrations of glycogen.[1] This may be of clinical significance because, from the evidence, these changes render the liver abnormally susceptible to injury.[2] The physiological effects of these two constituents may be interrelated, as suggested by the fact that the livers of individuals exposed to several hepatotoxins are not damaged when considerable amounts of glucose are administered.[3] This effect apparently is not due simply to the increased amounts of hepatic glycogen deposited, but to the fact that when adequate stores of carbohydrate are available for metabolic purposes, fatty infiltration of the liver is prevented.[4]

The abnormal hepatic chemical composition is particularly important in patients with gastrointestinal cancer because they frequently are subjected to considerable anesthesia, medication, and surgical manipulation. Since in normal individuals these procedures induce hepatic damage,[5, 6] it is reasonable to assume that the damage is considerably greater in a liver abnormally susceptible to injury because of its altered constitution.

In experimental animals, fatty infiltration of the liver can be reduced by the administration of certain dietary constituents. Moreover, the same measures apparently increase the functional capacity of the organ and its resistance to the usual injurious effects of several noxious agents.[7, 8] A clinical study, therefore, was undertaken to ascertain whether or not the preoperative administration of the same dietary factors to the patients with gastrointestinal cancer would restore the chemical composition of their livers to normal. The results of that study form the subject of the present report.

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Material

Thirty-seven patients with gastrointestinal cancer were studied. Of these, three had carcinoma of the terminal esophagus, 29 of the stomach, and five of the colon. As controls, 12 patients with benign gastrointestinal lesions were used. Of these, five had gastric ulcer, two atrophic gastritis, two gastric polyposis, one chronic ulceration of the terminal esophagus, and two ulcers of the duodenum. As a second control group, eight patients with obstructive lesions of the common bile duct were studied. In three this obstruction was due to carcinoma of the head of the pancreas, in four to impacted gall stones, and in one to a stenosis of the ampulla of Vater.

The final diagnosis in all patients was made at laparotomy and by microscopic examination of the biopsied lesion.

Methods

The preoperative care, dietary régime, and anesthesia of all patients, as well as the technics by which the liver tissues were obtained and analyzed have been reported previously.[1]

At 10 p.m. of the night before the day of operation, a small Levin tube was inserted into the stomach of each patient. This tube was allowed to remain in place until 7 a.m., and through it were introduced, every two hours for five doses, the test materials studied. At 7 a.m., one hour after the last tube feeding, the stomach contents were aspirated and discarded.

The glucose was administered in the form of 200 ml. of 25 per cent solution, so that in the five doses 250 gm. were given. The lipocaic employed was made according to the directions of Dragstedt,* and introduced through the tube in 1.6 gm. amounts suspended in 100 ml. of water. A 10 per cent aqueous solution of choline chloride was administered in five doses each of 0.6 gm. Inositol † was given in 240 mg. amounts five times, total 1,200 mg.

Results

The results are presented in four parts as the effects of the preoperative administration of (*a*) glucose, (*b*) lipocaic, (*c*) choline chloride, and (*d*) inositol on the chemical constitution of the livers studied.

A. Glucose: For a group of 18 fasted patients with gastrointestinal cancer, the hepatic glycogen previously was found to average 2.91 gm. per cent,[1] the fat 17.47 gm. per cent, and the protein 16.17 gm. per cent (table 1).

In contrast to these values were those of the livers of a group of 11 patients with gastrointestinal cancer who received preoperatively 250 gm. of glucose (table 2). In these, glycogen varied from 2.3 to 9.95 gm. and averaged 4.39 gm. per cent or 1.4 times that of the fasted control patients. The fat ranged from 3.9 to 15.2 gm. and averaged only 7.24 gm. per cent, or

* Procured through the courtesy of Eli Lilly & Co., Indianapolis, Ind.
† Procured through the courtesy of Lederle & Co., Pearl River, N. Y.

TABLE I

The Chemical Constitution of the Livers of Fasted Patients

Number of Patients	Disease	Concentrations of Hepatic					
		Glycogen, gm. per cent		Fat, gm. per cent		Protein, gm. per cent	
		Range	Average	Range	Average	Range	Average
18	Gastrointestinal carcinoma	1.0–7.3	2.91	5.3–35.0	17.47	12.9–17.95	16.17
4	Bile duct obstruction	1.3–5.1	2.62	11.5–26.6	17.72	12.3, 14.9	
4	Benign disorders of gastrointestinal tract	1.3–3.55	2.28	6.2–17.0	11.8	11.4–16.6	14.6

TABLE II

The Chemical Composition of the Livers of Patients with Gastrointestinal Cancer Who Received Preoperatively 250 gm. of Glucose

Patient	Histologic Appearance of Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent	Total Protein, gm. per cent
M. K.	Normal	4.2	8.1	13.8
B. V.	Normal	9.95	6.1	11.9
R. G.	Normal	3.1	15.2	17.9
T. C.	Normal	4.7	5.7	14.2
C. C.	Normal	3.0	5.4	15.9
A. A.	Normal	3.2	7.3	15.8
O. W.	Normal	4.5	4.55	16.3
O. B.	Normal	2.5	3.9	15.1
W. G.	Normal	5.2	4.7	
J. M.	Normal	5.6	10.3	17.0
A. W.	Normal	2.3	10.3	
	Average	4.39	7.24	15.32

0.42 that of the fasted control group. Of the 10 patients fed glucose, three still had abnormally high concentrations of liver fat (greater than 8.5 gm. per cent).[9]

In nine of the 11 instances in which the protein contents of the livers were determined, these were found to range from 13.8 to 17.9 gm. and average 15.21 gm., or about equal to that of the group of patients who received no glucose.

The preoperative ingestion of glucose apparently affected the chemical constitution also of the livers of patients with obstructive bile duct disease. In the preceding study the hepatic glycogen concentrations of four individuals with this disorder who were fasted before operation, averaged 2.62 gm. per cent, the fat averaged 17.72 gm. per cent, and the protein 13.5 gm. per cent (table 1).

Four individuals with common bile duct obstruction were given preoperatively 250 gm. of glucose. The glycogen values varied from 2.4 to 4.6 gm. and averaged 3.05 gm. per cent, or 1.2 times that of the fasted controls.

The concentrations of fat in their livers were found to range from 3.8 to 8.85 gm. and average 6.40 gm. per cent, or 0.31 that of the fasted group. No significant difference was found between the contents of protein in the livers of the fasted and of the patients treated with glucose (table 3).

TABLE III

The Chemical Composition of the Livers of Patients with Bile Duct Obstruction Who Received Preoperatively 250 gm. of Glucose

Patient	Histologic Appearance of Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent	Total Protein, gm. per cent
L. H.	Bile stasis, periductal fibrosis	2.8	6.95	12.2
L. L.	Atrophy, central pigmentation	4.6	8.85	14.5
L. I.	Bile stasis	2.4	6.0	12.5
M. W.	Atrophy, bile stasis	2.4	3.8	13.0
	Average..	3.05	6.40	13.00

Similar studies were made in a group of patients with benign gastrointestinal disorders. In the livers of four fasted patients previously reported the glycogen averaged 2.28 per cent, the fat 11.8 gm. per cent, and the protein 14.6 gm. per cent (table 1).

In contrast, in a group of six patients with benign disorders who were fed preoperatively 250 gm. of glucose, the hepatic concentration of glycogen was found to be considerably increased. These values ranged from 5.25 to 9.45 gm. and averaged 7.35 gm. per cent, or 3.4 times that of the control group (table 4). It is interesting to note that the average increase of glycogen in the livers of patients with benign gastrointestinal lesions who received glucose preoperatively is considerably greater than that of patients with gastrointestinal cancer or obstructive biliary disease who received the same amount of carbohydrate.

TABLE IV

The Chemical Composition of the Livers of Patients with Benign Gastrointestinal Disorders Who Received Preoperatively 250 gm. of Glucose

Patient	Histologic Appearance of Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent	Total Protein, gm. per cent
F. H.	Normal	6.2	2.3	14.3
J. S.	Normal	7.0	6.35	11.4
A. H.	Normal	9.45	6.2	
J. H.	Normal	7.0	7.85	15.8
D. E.	Normal	9.2	8.5	
A. U.	Normal	5.25	5.95	
	Average..	7.35	6.19	13.80

The fat content of the livers of the six glucose-treated patients with benign disorders ranged from 2.3 to 8.5 gm. and averaged 6.19 gm. per cent, or 0.53 times that of the control group. The protein concentrations ranged from 11.4 to 15.8 gm. and averaged 13.80 gm. per cent (table 4), a value equal to that of the fasted group.

Hence, the preoperative ingestion of glucose by the three groups of patients studied decreased the content of fat in their livers. The stores of hepatic glycogen were markedly increased only in the patients with benign gastrointestinal disease, a fact which suggests that hepatic glycogenesis or glycogen storage in patients with gastrointestinal cancer is impaired. These individuals are known to have hepatic dysfunction but no morphologic liver damage.[1] Extensive impairment of glycogenesis or glycogen storage apparently exists, too, in the patients with common bile duct obstructions who are known to have both functional and anatomic damage. Finally, the ingestion of glucose was without significant effect on the protein concentration in the livers of the three groups of patients studied.

TABLE V

The Chemical Composition of the Livers of Patients with Gastrointestinal Cancer Who Received Preoperatively 8 gm. of Lipocaic

Patient	Histologic Appearance of Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent	Total Protein, gm. per cent
H. D.	Normal	1.6	9.3	
A. McH.	Normal	4.3	7.45	
H. B.	Normal	1.6	6.9	
A. v. V.	Normal	3.6	7.2	
H. M.	Normal	2.4	9.35	
F. S.	Normal	2.25	11.1	
S. H.	Normal	2.9	7.35	15.2
S. F.	Normal	2.9	7.0	18.7
A. E.	Normal	1.8	7.8	14.5
H. H.	Normal	2.5	4.05	
A. U.	Normal	3.5	11.1	
	Average..	2.67	8.05	16.13

B. Lipocaic: The administration of lipocaic to animals with fatty infiltration of the liver effectively reduces their abnormal concentrations of hepatic lipid.[10] Whether the lipotropic effect of this material is due to its content of choline and inositol * or to some other factor still is unknown. The effects of this lipotropic material on the fat content of *human* livers thus far have not been ascertained. Were it possible by this means to decrease the excess fat content in the livers of patients subjected to hepatotoxins and surgical operations, a valuable therapeutic agent might be at hand for the prevention of liver damage.

Eight grams of lipocaic divided into five equal doses were administered to a group of 11 patients with gastrointestinal cancer during their last 10 preoperative hours. The concentrations of fat in the livers of these individuals were found to range from 4.05 to 11.1 gm. and average 8.05 gm. per cent, or only 0.46 that of the group of 18 fasted patients with the same disorders. Of the 11 patients who received lipocaic, only four had slightly

* The choline and inositol contents of the lipocaic used were found to be 2.6 and 3.5 per cent respectively. These determinations were made for us by Dr. W. Wooley of the Rockefeller Institution of Medical Research and by the Laboratories of the Standard Brands, Inc.

abnormal concentrations of liver fat. The administration of lipocaic apparently had no significant effect on the concentrations of hepatic glycogen in these individuals, but, of course, no such effect was expected (table 5).

The concentrations of lipid in the livers of two patients with benign gastrointestinal lesions who each received 8 gm. of lipocaic preoperatively were 7.9 and 9.8 gm. per cent (table 6). Four patients with obstruction of the common bile duct were treated similarly and only two had normal hepatic concentrations of lipid. These concentrations in the four patients were 7.85, 8.4, 12.7, and 19.5 gm.

TABLE VI

The Chemical Composition of the Livers of Patients with Benign Gastrointestinal Disorders Who Received Preoperatively 8 gm. of Lipocaic

Patient	Histologic Appearance of Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent
F. N.	Normal	1.5	9.8
H. S.	Normal	3.0	7.9

It appears, then, that the administration of lipocaic to patients with gastrointestinal cancer subjected to operation significantly reduces the abnormally high content of fat in their livers. This did not uniformly occur in patients with obstruction of the bile ducts.

C. Choline Chloride: When it was apparent that the administration of lipocaic to patients with cancer of the gastrointestinal tract could reduce the concentrations of fat in their livers, it became of interest to ascertain whether or not this effect was due to the choline or inositol contents of the material. Both of these compounds are known to have a lipotropic effect in experimental animals.[11, 12]

TABLE VII

The Chemical Composition of the Livers of Patients with Bile Duct Obstruction Who Received Preoperatively 8 gm. of Lipocaic

Patient	Histologic Appearance of Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent
F. B.	Atrophy, bile stasis	3.3	12.7
L. S.	Bile stasis, periductal fibrosis	2.5	19.5
G. W.	Bile stasis, periductal fibrosis	2.8	8.4
E. T.	Bile stasis	1.1	7.85

Hence, seven patients with gastrointestinal cancer each were given a total of 3 gm. of choline chloride, or about 12 times the amount in the lipocaic administered. The concentrations of fat in the livers of these seven patients were found to range from 6.9 to 16.1 gm. and average 11.21 gm. per cent, or 0.64 that of the fasted patients (table 8). Of these seven values, four were above the upper limit of normal. Therefore, the lipotropic effect

of lipocaic was significantly greater than that of comparatively large doses of choline, and could not be attributed entirely to its choline content.

The administration of choline had no apparent effect on the hepatic concentration of glycogen.

TABLE VIII

The Chemical Composition of the Livers of Patients with Gastrointestinal Cancer Who Received Preoperatively 3 gm. of Choline Chloride

Patient	Histologic Appearance of Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent
P. R.	Normal	1.1	6.9
F. G.	Normal	2.3	11.0
F. L.	Normal	2.6	16.1
A. R.	Normal	2.7	8.2
H. B.	Normal	2.3	16.0
M. G.	Normal	4.74	8.3
T. S.	Normal	6.6	12.0
	Average..	3.19	11.21

D. Inositol: Inositol was given in five equal doses of 240 mg. to eight patients with gastrointestinal cancer. The total amount ingested by each was equal to four times that contained in the lipocaic administered. At the time of laparotomy the average hepatic concentration of glycogen was 3.28 gm. per cent. That of fat was 6.94 gm. per cent, or 0.39 that of the controls. In only one instance was the fat content abnormally elevated (table 9).

TABLE IX

The Chemical Composition of the Livers of Patients with Gastrointestinal Cancer Who Received Preoperatively 1.2 gm. of Inositol

Patient	Histologic Appearance of Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent
S. S.	Normal	4.95	4.55
M. McN.	Normal	3.0	6.7
R. B.	Normal	2.1	7.05
A. H.	Normal	4.25	16.7
A. W.	Normal	1.5	5.7
K. G.	Normal	3.2	5.6
M. L.	Normal	3.6	5.7
J. K.	Normal	3.6	3.5
	Average..	3.28	6.94

TABLE X

The Chemical Composition of the Livers of Patients with Benign Gastrointestinal Disorders Who Received Preoperatively 1.2 gm. of Inositol

Patient	Histologic Appearance of Liver	Glycogen, gm. per cent	Total Lipid, gm. per cent
F. S.	Normal	3.6	7.5
W. O.	Normal	2.9	7.0
S. S.	Normal	2.6	5.1
M. A.	Normal	3.2	4.9
	Average..	3.08	8.12

The same amounts of inositol also were administered preoperatively to four patients with gastric ulcer. The average glycogen content of their livers was found to be 3.08 gm. per cent and of lipid 8.12 gm. per cent (table 10).

The significantly decreased concentration of fat in the livers of the patients fed inositol suggests that the lipotropic effect of lipocaic may be due to its content of inositol. Experiments now are under way to ascertain the effect on the hepatic lipid of inositol in amounts just equal to that contained in the lipocaic administered, both when given alone and with choline.

Discussion

Previous studies have indicated that excessive lipid deposition in the livers of experimental animals can be prevented by the administration of carbohydrate [4] and of certain lipotropic factors.[10] It was reasonable to assume, therefore, that these measures also could reduce the lipid infiltration in the livers of human beings. This assumption now has been borne out by the data presented. The preoperative administration of glucose was found to exert a significant lipotropic effect on the liver fat of all patients studied, even though it did not increase significantly the hepatic glycogen stores in the patients with gastrointestinal tract cancer or with common bile duct obstruction. However, there is considerable evidence that the mere presence of hepatic glycogen stores does not necessarily afford protection to the liver nor is it always associated with a decreased content of hepatic lipid. The liver with a large store of glycogen but infiltrated with fat ordinarily is readily susceptible to damage, whereas the liver with depleted glycogen stores but with a low lipid content withstands the deleterious effect of many hepatotoxins. It would appear that it is the metabolism of carbohydrate which provides the organ with its increased resistance.[4]

It is of considerable interest to note that the administration of carbohydrate to patients with benign gastrointestinal disorders increased their hepatic glycogen stores considerably more than it did those of patients with gastrointestinal cancer or with bile duct obstruction. Conceivably, this difference could be due to (*a*) a decreased ability of patients with gastrointestinal cancer and bile duct obstruction (patients with considerable hepatic dysfunction) to absorb the administered glucose from their alimentary tracts, or (*b*) a decreased capacity of their livers to form or to store glycogen. Data obtained from routine oral glucose tolerance curves do not indicate that impaired absorption of carbohydrate from the alimentary tracts of patients with gastrointestinal cancer or obstructive biliary lesions would explain the abnormality.[13] On the other hand, it is known that these patients have a considerable degree of hepatic insufficiency [14] and that since it is a function of the liver to synthesize and to store glycogen, probably that function also has been damaged. The possibility should be entertained, however, that the limited capacity of the livers of these individuals to lay

down glycogen might be due to a derangement of those endocrine factors concerned with glycogenesis.[15]

It now appears that lipocaic exerts its lipotropic effect not only in experimental animals but also in human beings. Therefore, this material should prove useful in the preoperative preparation of patients with gastrointestinal cancer in order to decrease the susceptibility of their livers to the damage ordinarily sustained from surgical manipulation, operative anesthesia, and the necessary administration of those drugs detoxified by the liver.

The effect of the lipocaic apparently is not entirely due to its choline but may be due to its inositol content. Experiments now are under way to ascertain the lipotropic effects of (1) the amount of inositol equal to that in the 8 gm. dose of lipocaic, both when administered with and without choline, (2) smaller amounts of lipocaic, and (3) various proteins and amino acids. The results of these studies will be reported later.

Summary

1. The administration of glucose increased the hepatic glycogen stores significantly only in the patients with benign gastrointestinal disorders.

2. The preoperative oral administration of glucose to patients with gastrointestinal cancer, common bile duct obstruction, and with benign gastrointestinal lesions, significantly decreased the concentration of fat in their livers.

3. The administration of glucose did not affect significantly the concentration of hepatic protein in the three groups of patients studied.

4. The administration of lipocaic significantly decreased the content of fat in the livers of patients with gastrointestinal cancer. This effect could not be explained entirely by the choline content of the lipocaic, but may be due to its inositol content.

5. The ingestion of lipocaic did not affect significantly the concentrations of glycogen or protein in the livers of the three groups of patients studied.

6. It is suggested that patients who frequently come to operation with fatty infiltration of their livers (as do those with gastrointestinal cancer and bile duct obstruction) should be given preoperatively glucose and lipocaic in order to restore toward normal their altered hepatic chemical constitution. By these means it might prove possible to increase the resistance of their livers to damage by hepatotoxins.

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BRONCHIAL ASTHMA: CLASSIFICATION BASED ON ETIOLOGICAL AND PATHOLOGICAL FACTORS*

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THERE are many classifications of bronchial asthma to be found in the literature. Their number and the difficulty in classifying many patients under them indicates the necessity for a reclassification. This should be based on (*a*) a knowledge of the pathology of the disease, (*b*) the mechanisms involved in the production of the pathologic changes and (*c*) the symptoms produced thereby.

As early as 1868 [1] Hyde Salter separated bronchial asthma from other conditions which simulated it and attempted an etiological classification which is copied below.

TABLE I

Provocation of asthmatic paroxysm	Affecting the air tubes primarily Intrinsic	Things inhaled	Certain kinds of air Chemical and mechanical irritants Animal emanations
		Inflammation of air passages	
		Offending condition of the blood	After all food From certain ingesta From dyspepsia
	Applied to some remote part	Reflex nervous	Through the organic nervous system Through the cerebro-spinal system
		Central nervous Irritation	Irritant psychical Irritant physical

The terms intrinsic and extrinsic as used by Salter refer to the bronchial tree. Those cases in which the causes operated directly on the air passages were called intrinsic; those in which the causes operated indirectly to produce symptoms were called extrinsic.

In 1918 I. C. Walker [2] extended the etiological classification on the basis of the results of skin tests with protein extracts. He used the terms extrinsic and intrinsic in a manner opposite to their use by Salter, the terms referring to the patient and not the bronchial tree. This use of these terms is generally accepted today. Cases in which positive skin reactions could be obtained were considered to be due to causes entering the body from without and were, therefore, called extrinsic. Those cases in which the causes were

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considered to be within the body were attributed to bacterial sensitivity and were called intrinsic. About half of Walker's cases fell into each group. Later (1927) Rackemann [3] classified 1,074 patients etiologically on the basis of skin tests, the history, the physical findings, and the clinical course in each patient. One hundred and fifty were unclassifiable; the remainder were divided almost equally into the extrinsic and intrinsic groups as defined above. Both Rackemann and Walker were unable to find regular differences in the clinical manifestations which would enable them to separate the cases into groups without prolonged observation of the individual patients.

My own experiences and studies during the past 20 years have confirmed me in the belief that *bronchial asthma has a distinct pathology, and that the characteristic pathological changes are present in patients who are ultimately shown to have either extrinsic or intrinsic etiological factors, or in whom the etiology remains a mystery.* If one rules out those cases in which obstructive dyspnea is caused by a foreign body, tumor, or infectious inflammatory exudate within the bronchial tree, those due to pressure of tumors or aneurysm from without the bronchial tree, and dyspnea due to cardiac failure, the remainder will be found to have the changes which will be described below as the basic variation from normal. This statement does not imply that these changes are necessarily permanent, and that they will necessarily be found in persons who may die from some unrelated disease or accident between attacks. *They can always be demonstrated during attacks, and in those who die in them.*

In 1932, Kline, Cohen, and Rudolph [4] reported their observations on the histology of experimentally induced allergic reactions in man. In all, 32 biopsies of skin were studied. The tissues were removed at intervals of from five minutes to 22 hours after the allergen was injected. In each instance a biopsy of a histamine reaction was removed from the same patient for comparative study. These studies showed that the reaction to histamine and to plant and animal foreign protein allergens was the same, no matter how dissimilar the allergens were. The reaction consisted of edema of the superficial layers of the dermis, with an acute inflammatory reaction beginning around the blood vessels. In sections of tissue removed in less than one hour, eosinophiles were the predominant cells, accounting for 90 per cent of the exudate. Later these tend to disappear and polymorphonuclear neutrophiles and mononuclear phagocytes appear. Sections of tissues removed three hours or more after intradermal injection of the allergen show changes indistinguishable from those seen in ordinary inflammation. This observation explains the divergent opinions of various pathologists in their interpretation of such lesions, as those found, for example, in nasal polyps. Gillies [5] examined nasal polyps and divided them into two groups, allergic and infectious, on the basis of the finding of eosinophiles. About half were in each group. It is probable that all were allergic, but that in half the tissues were removed at too long an interval following the last allergen contact.

The only conditions which produce histological changes which might be confused with these allergic reactions are infestations with the various animal parasites. In these conditions the lesion is probably produced by an allergic mechanism similar to that just described, as it is well known that immediate skin reactions are obtained after intradermal injections of saline extracts of the causative agents.

Examination of the nasal and sinus mucosa in allergic rhinitis, of mucous polyps and of the bronchial mucous membranes in bronchial asthma show the characteristic findings. In the experimental study referred to above it was demonstrated that considerable inflammatory reaction remained in the tissues underlying the area in which the wheal was produced at 22 hours. When new reactions are instituted in areas which have not recovered completely from previous ones, more chronic lesions are produced. It is in this way that the hyperplastic and polypoid changes in the nasal and sinus mucous membranes develop. The mucous gland and muscle hypertrophy, the thickened basement membrane and the more chronic changes seen in bronchial asthma are produced in a similar manner.

The histological picture of induced allergic reactions varies in intensity, depending on the tissue reactivity and the concentration of allergen, from a very mild inflammatory reaction without tissue destruction to lesions which show areas of necrosis which will be replaced ultimately by fibrous tissue. These severe reactions resemble in all respects those originally described by Arthus,[6] and referred to in the literature as the Arthus phenomenon.

When the description of the morbid anatomy found in bronchial asthma as first reported by Huber and Koessler [7] is studied in the light of the foregoing, it is possible to explain all of the changes or variations of the characteristic allergic reaction.

The fact that the clinical and histological picture of the clinical allergies is the same for reactions induced by all plant and animal foreign proteins and drugs indicates that some common toxic substance is responsible for all of them. This substance could be formed only from the tissues themselves, and the work of Dragstedt,[8] Katz,[9] Rose,[10] Katz and Cohen,[11] and others indicates that it is pharmacologically indistinguishable from the H substance first described by Thomas Lewis.[12] This conception does not predicate that H substance is necessarily histamine although histamine or histamine-like substances certainly play a part.

The release of H substances is one of the fundamental cellular mechanisms of the body. These substances are released as a result of cell irritation which may be brought about by many different stimuli. The allergen antibody reaction of allergy is only one such stimulus. Cholinergic drugs such as eserine induce H substance reactions which are indistinguishable from those seen in allergy and mimic in every way, including the refractory period, those produced as a result of allergen antibody combination. In addition, as previously pointed out, both reactions are indistinguishable from a histamine reaction.

TABLE II

Allergen Antibody Stimulus	H substance reaction in bronchial mucosa	Extrinsic	Allergen demonstrable	Begins in early life. Family history positive. Other allergic manifestations common. Skin tests positive or allergen demonstrable by environmental control. Complete remission between attacks. No organic changes. Prognosis for relief and prevention of future attacks good. Seldom die of asthma. No effect on longevity.
			Allergen not demonstrable	
Cholinergic Stimulation		Combined extrinsic and intrinsic	Primary extrinsic with intrinsic complications	organic complications
				functional complications
			Primary intrinsic with extrinsic complications	organic complications
				functional complications
Unknown Stimulus		Intrinsic		Begins around 40 years of age; family history usually negative. Other allergic manifestations uncommon. Skin tests negative—Allergen not demonstrable by environmental control. No complete remissions. Organic changes common. Prognosis for relief and prevention of future attacks poor. Prognosis as to life grave. Many die of asthma. Profound effect on longevity.

Consideration of those observations and discussion indicates that bronchial asthma should be considered to be the symptoms and signs resulting from H substance reactions in the bronchial tree. The cases may be divided into two large groups:

(1) Extrinsic, in which the allergen can be demonstrated to enter the body from without and

(2) Intrinsic, in which the reaction results from some internal stimulus.

Cases which belong primarily to either of these large groups may develop either organic or functional complications which require their classification into a third group, combined extrinsic and intrinsic.

The following chart illustrates this classification and gives the salient points in the life history of the cases which fall into the two major divisions (chart 2).

It is not difficult to classify most asthmatics into one or the other of these large groups once one becomes familiar with their characteristics and such a separation is imperative. The management of extrinsic asthmatics is a comparatively simple matter since the etiological factors can usually be determined and their avoidance or immunization against them is effective in preventing attacks. A great deal of physicians' time and patients' time and money is wasted, however, if the intrinsic asthmatics are not recognized since the methods useful in the study and special treatment of extrinsic asthmatics are of little or no value in those of the intrinsic group.

Every well read physician is familiar with the life history of the typical extrinsic asthmatic and reference to table 2 will remind us of the characteristics of this condition. It is not so well known, however, that a diagnosis of intrinsic asthma can be made by clinical means, because of the history and clinical characteristics of this condition, without recourse to laboratory aids such as skin tests except as confirmatory evidence.

Characteristically, intrinsic asthma begins at about 40 years of age with a dry spasmodic cough. At first the cough is not very troublesome, and relief is not sought until the paroxysms of cough become more frequent and wheezing and slight dyspnea occur. These symptoms gradually become more pronounced and recur more frequently and within a period of from a few months to two years, the first attack of typical asthma occurs. The asthmatic attacks, once they are established, recur almost daily and there is seldom complete freedom from cough, wheezing, or both, between them. Nasal symptoms are much less common than in cases of extrinsic asthma, although nasal and sinus polyposis are common findings. Skin tests with common allergens are uniformly negative. Environmental control in filtered air is not followed by complete relief from symptoms. Many intrinsic asthmatics are allergic to drugs such as acetyl salicylic acid; their attacks can be precipitated by the administration of these drugs, but their elimination is not followed by complete relief from symptoms.

Since these patients have continuous allergic reactions in their respiratory mucous membranes and elsewhere, chronic changes occur, and it is in this group particularly that the changes are likely to be irreversible and to lead to permanent tissue changes. Emphysema, cylindrical bronchiectasis, hyperplastic sinusitis and polyposis appear early and are usually present in some degree when the patient first seeks relief. The irreversible nature of the lesions leads to gradual encroachment on the reserve capacity of many of the parenchymatous organs, and since the blood vessels themselves are often the seat of the lesions, periarteritis nodosa is not an uncommon terminal clinical or pathological diagnosis. Most of the deaths in asthma attacks occur in this intrinsic group, and in my opinion it is this group which is responsible for the high rate of death after 40 years which is recorded in the experiences of the insurance companies.

Because of the severity of allergic lesions and their chronicity there is a widespread demand for eosinophiles and blood eosinophilia is very common in intrinsic asthmatics.

Intrinsic asthma might be called "asthma gravis." Once the condition is well established there is a gradual downward course in a typical case and death may occur in from a few months to several years. In some patients, however, the course is much less rapid and these may run a course not unlike those with extrinsic asthma. Since the etiological factors are at present unknown, the prevention of attacks by the removal of the offending allergens, or immunization against them, cannot be carried out. Further knowledge of this condition awaits new methods of study to determine the etiological factors.

Summary

1. A classification of bronchial asthma based upon pathological and etiological factors has been outlined.

2. All true asthmatics have lesions resulting from H substance reactions in the bronchial mucosa.

3. The pathology of these lesions is the same in all true asthmatics.

4. Cases of asthma fall into two large groups which can be divided clinically into extrinsic and intrinsic.

5. Present day methods enable us to manage cases of extrinsic asthma fairly well. Cases of intrinsic asthma must be recognized. They may then be studied as a separate group and perhaps the etiological mechanisms may be elucidated.

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MIGRAINE HEADACHES RELIEVED BY HYPOGLYCEMIC REACTION; REPORT OF TWO CASES *

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In the course of treating opiate addicts by hypoglycemic reactions [1] two patients were encountered whose addiction resulted from treatment for recurrent headaches. These headaches had not responded to the remedies usually used to relieve attacks of migraine. Such remedies as gynergen,‡ pure oxygen, with 7 per cent CO_2, vitamin B_1 intravenously, histamine desensitization, and hormone injections were either only partly successful or useless. The recurrent headaches were apparently accepted as an unavoidable condition; the primary complaint was the addiction. It was, therefore, impressive to all concerned, when in the course of treating withdrawal symptoms, intervening headaches were promptly aborted. Previously, only an opiate could produce such complete relief. One patient, quite in keeping with his personality, preferred to believe that the headaches during the first few days in the hospital were due to opiate craving rather than migraine. Not until two weeks later when he underwent a typical attack did he admit the efficacy of the treatment. Two additional attacks were likewise promptly relieved.

The method of treatment was essentially that described for the treatment of addiction [1] and neurodermatoses.[2] The dosage of insulin varied from time to time, the gauge was a systemic reaction manifested clinically by diaphoresis, thirst, somnolence and hunger. In a favorable reaction the pupils were small and the pulse rate reduced. Coma or loss of consciousness was not required. Intravenous administration of the insulin seemed to produce the desired effect in approximately one half the time usually required after an intramuscular injection, provided the dosage was adequate to produce the indicated physiologic effects.

Case Reports

Case 1. A married woman, age 30, was admitted to the hospital December 28, 1941, for treatment of addiction to morphine and dilaudid. The family history was non-contributory, except that a maternal aunt had suffered from recurrent headaches. The patient, oldest of four siblings, had been healthy until the onset of her present complaints. Early growth and development were quite normal. Following the birth of her second child she suffered a period of menorrhagia and had two pelvic operations resulting in oöphorohysterectomy in 1937. Six months later she began suffering from severe recurrent headaches. Ordinary analgesics and gynergen failed to provide relief. Histamine desensitization had no effect on the intensity or frequency of the

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‡ Ergotamine tartrate.

headaches. She was then given opiates. In one attack, which lasted three days, a total of 7 grains of morphine was administered in divided doses. After this she was placed on 15 to 20 thousand units of theelin per week. The headaches were very much attenuated for about eight months, requiring only an occasional dose of codein. Gradually the severity of the headaches increased so that morphine was often required. In June, 1941 she was ordered to take 10,000 units each of theelin and amniotin nightly. This again, apparently, reduced the severity of the attacks for about three months. At this time she experienced a nervous shock because her husband was badly injured in an automobile accident. During the trying period which followed, the hormone injections were ineffective and addiction to dilaudid was established. She took 1/16 gr. dilaudid three to four times per day, in addition to the hormone medication, for months prior to admission to the hospital.

The headaches consisted of throbbing, pressure and hyperesthesia over the vertex of the head. Nausea, occasional retching, preceded and often continued throughout the attack. She did not experience any prodromal symptoms. During the intervals she felt well and enjoyed working in her husband's dental office. The headaches came suddenly, without any time relationship, except that nervous strain was likely to bring on an attack.

Symptoms of opiate abstinence disappeared within four days. During the second night in the hospital she had a severe attack of headache which she was sure only an opiate could relieve. She and her husband, who was present at the time, were surprised and grateful when the headache stopped in about half an hour after an injection of insulin. A less severe attack during the second week was similarly relieved. The hormone medication which she had brought with her was not used nor were analgesics or sedatives necessary at any time. The husband and the patient were fully convinced that hypoglycemic reactions could stop attacks of headaches for the patient. She left the hospital January 11, 1942.

She felt well at home for six weeks when the headaches recurred. Ten days before readmission, April 14, the headaches were so severe and protracted that she returned to the use of dilaudid. She was soon frightened at the prospects of renewing the addiction and came by plane for assistance.

In the absence of the writer, another physician gave her some dilaudid the first night and from April 15 to 20, induced mild hypoglycemic reactions once daily. The headaches stopped on April 18, without further use of an opiate. This physician believed that his daily interviews with the patient were probably more useful than the insulin injections. On April 22, while at the village movie, she suddenly had an attack and had to rush back to the hospital. Still another physician on duty at that time gave her 40 units of insulin and allowed, according to the patient, "a good reaction" to occur. The headache was completely relieved by this one treatment. Some days later, when the author returned to duty, the patient stated that the injections given by the first physician were exceedingly mild; they made her more comfortable but were not as effective in stopping the headache as the injection given by the other physician. Until April 28, the day she returned to the author's supervision, she was taking nightly injections of theelin and amniotin, 10,000 units of each. This was promptly discontinued. She had taken these injections during the entire period at home, on the advice of a consultant, after her first discharge from the hospital. During the remainder of her stay, no further hypoglycemic therapy was necessary. A moderate headache developed on the evening of May 27, which lasted all the next day. No special treatment was administered because the patient preferred to see it through without help. She was making preparations to return home and wanted the assurance the headaches would not prove disabling. She believed the headache might have been due to the excitement incidental to departure. She left for home in a buoyant and hopeful state of mind.

A letter from the husband, four months later, reported her health good, that she enjoyed devoting her time to home duties, and that she had not had any severe headaches. During the first month home she was hospitalized for the excision of multiple cystic abscesses on the buttocks. She passed through a general anesthetic and the postoperative period without any headaches. Ordinarily, such an ordeal would have caused her to have a severe attack of migraine.

Comment: Patients recently treated for opiate addiction should be discouraged from using hypodermic medication. They have a difficult time of it for some months, without providing a teasing reminder. Although psychotherapy deserves some credit for the successful management of this case, it would have failed without hypoglycemic therapy. There may be some doubt about the diagnosis of migraine in this patient. Knowing the multifarious nature of the clinical entity and the lack of unanimity as to etiology and pathologic or physiologic basis thereof, the question is academic. It is unusual for migraine to develop after the menopause, but such cases are known.[4] The fact of its relation to emotional or nervous disturbance occurring in a woman and recurrent without a demonstrable pathologic lesion, plus evidence of some hereditary influence, favors the diagnosis of migraine.

Case 2. A married man, age 39, was admitted May 17, 1942, as a morphinist incidental to treatment for migraine. He described his father as of "Hungarian temperament." The mother suffered from migraine for many years, also nervousness and hypertension for the last 15 years of her life. A paternal uncle had migraine. The patient was the only one of seven siblings subject to recurrent headaches. His health had always been good except for a period before and after a nephrectomy at 23. At the age of 18, after his father died, he felt obliged to abandon school and go to work. He clerked for a number of years while furthering his education by attending night school. He became a licensed insurance broker at 25 and had been in business for himself since then. He married at 34, only after his mother had died and after all the other siblings had married, because he felt responsible for the settling of the whole family group. His marriage was congenial. He thought of his wife as an understanding person, yet there was an agreement against having offspring and she continued teaching in the public school system. He hoped to retire at 50, to take it easy and enjoy life, just he and his wife. He described his own personality as, "I'm kind of a Dr. Jekyll and Mr. Hyde." Socially he was friendly, jolly, and a life-of-the-party fellow, while in business he was a "technical person," "very serious," "definitely business before pleasure," ambitious and determined to succeed. Objectively, he impressed one as a benevolent egotist, demanding and assertive, emotionally labile with an explosive temper.

One day in his office, about seven years previously, he felt nauseated and then developed a terrific pounding on the left side of his head. It did not subside until a physician gave him a hypodermic injection. Several weeks later he had another attack. The headaches recurred at four to six week intervals—always nausea, occasionally dizziness, and occasionally vomiting. The headaches were always on the left side, the pain made unbearable by rhythmic spasms on the side of the head. He consulted many neurologists, had several "complete check-ups," and numerous medications were tried. He received intramuscular and intravenous injections of gynergen, intravenous injections of vitamin B_1, inhalations of 100 per cent oxygen, and oxygen with 7 per cent CO_2, histamine desensitization, and many analgesics and sedatives without adequate relief. Gynergen aborted some of the headaches if the injections

were taken early. It often failed, and morphine had to be given later. Gynergen caused a tightening of his nerves, especially a constriction around the throat, and aggravated the nausea. The need for morphine increased as he began to use it at the first signs of an impending headache. During the year preceding admission he took daily 3/4 gr. to 1 gr. morphine or its equivalent in dilaudid, in divided doses. He tried several times to break the habit through voluntary abstinence but failed repeatedly because he would get very ill.

In the hospital he was treated with insulin for four days until free of withdrawal symptoms. In this period he had two severe headaches which were promptly relieved. From the fourth day on he enjoyed the stay in the hospital, had a good appetite, enjoyed diversion during the day and slept well at night without the aid of any medication. He was not convinced insulin could relieve his migraine headaches until May 30. He thought the headaches during the first few hospital days were part of the withdrawal syndrome. On May 30, at 11:00 p.m., one of his typical attacks began. When seen a half hour later he seemed in great agony, especially as he felt the spastic griping on the side of his head, occurring at intervals of a minute or two and lasting 15 to 30 seconds. During these spasms he was unable to talk, writhed with pain, and thrashed around on the bed. He was given an intravenous injection of 40 units of insulin. In about 10 minutes the spasms lessened in frequency and intensity. Another 10 minutes later he reached for a cigarette with the remark, "If I feel like helping myself to a cigarette, you can be sure I am much easier." For the next half hour he was rather talkative, slightly euphoric and praised the treatment profusely. At 12:15 a.m. he felt very hungry; the headache had entirely disappeared. After taking fruit juice and a lunch of toast, jam and milk, he was soon asleep. He slept soundly until awakened at 6:30 a.m., feeling none the worse for the experience the night before.

He felt completely well until June 11, the day before leaving the hospital. After lunch, this day, he reported having migraine since the forenoon. The headache was relieved within an hour by an injection of insulin. In the evening he had a much more severe attack. When seen at 9:30 p.m. he seemed very much distraught from suffering. Although the headache was somewhat abating, he felt very nervous and was sure he would not be able to sleep. He was given an intravenous injection of 60 units insulin. When seen again at 11 p.m. he was in a fairly active hypoglycemic reaction and felt entirely free from headache and nervousness. The hypoglycemia was terminated with fruit juice and a lunch. He slept well and awakened the next morning in high spirits, prepared to leave the hospital. He thought the headaches might have been due to a business matter pending in the office. His personal physician reported five months later that the patient had successfully gone through an emergency appendectomy, five or six attacks of migraine which were relieved by intravenous injections of insulin, and apparently remained free from the opiate addiction.

Comment: This is unquestionably a case of migraine and equally certain is the effectiveness of hypoglycemic reaction in relieving individual attacks. It is a proper question whether the accessibility to opiates, present in both cases, did not contribute to their refractiveness to other remedies. Once the relief by morphine is experienced for a specific complaint nothing else can be quite as satisfactory, except perhaps a hypoglycemic reaction. The use of opiates for any recurrent ailment makes the remedy more of a liability than the disease. Irrespective of whys or wherefores, both patients reached addiction to opiates because other remedies were unsuccessful in relieving the headaches.

Discussion

Migraine has been known for centuries, but more recently it is thought of as a syndrome rather than a disease. Wilson and Bruce [3] discuss the outstanding views on the pathogenesis of migraine. They find exceptions and faults with all of them. They state, "As yet the precise nature of the disturbance of function underlying migrainous symptoms has not yet been clearly exposed," and believe the heritage of the migrainous individual is "a sensitive mode of reaction on the part of the cranial neurovascular system to stimuli of extreme diversity." Bing and Haymaker [4] can offer no more than to state that one of them has "been accustomed to regard migraine as a vasoconstrictor neurosis." In the current literature the controversy seems to hinge on whether the attack is due to a vasoconstrictor or vasodilator action of the sympathetic nervous system. Yet, therapeutically, both vasoconstrictor and vasodilator drugs have proved effective in aborting attacks in some cases. Sutherland and Wolff [5] have demonstrated migraine is due to dilatation and distention of the cranial arterial walls. They find "the therapeutic effect of gynergen depends on its ability to produce prolonged and powerful vasoconstriction." Solomon [6] who studied the action of gynergen in non-migrainous individuals, finds "migraine is not a disease caused by general sympathetic dysfunction." Graham and Wolff [7] have shown graphically that gynergen reduces the amplitude of arterial pulsations and the speed of recovery coincides with this action of the drug.

The etiologic factors generally recognized as contributing heavily to migraine attacks are a hereditary predisposition and abnormalities "deeply hidden, principally in the glands of internal secretion, in the sympathetic nervous system and in the emotional personality make-up of the individual." [8] Alvarez [10] finds most patients "are overly reactive to emotion and overly sensitive to all stimuli," highly conscientious and restless individuals "who are always overworking or worrying or taking life too seriously," and above average intelligence, ability and drive. Lack of stability and self-discipline causes waste of the latter attributes. It is, therefore, to be expected that migraine sufferers would benefit from psychotherapy, especially a distributive analysis dealing with immediate problems and personality adjustments. This is precisely what many observers have found. Migrainous persons are often ill adjusted, rigid, repressed perfectionists lacking in average "normal" outlets for their emotions. Alvarez finds sympathetic interviews and understanding preferable to elaborate and expensive examinations. Lennox suggests that "main reliance must be placed on the gradual education of the patient so that he will adjust his work and his methods of living to the personality and the nervous system which he has inherited."

Among migrainous patients there is a strong diathesis to allergic reactions. von Storch [9] reports 76 per cent of 862 cases significantly allergic. O'Sullivan [11] claims 70 per cent of migrainous individuals have positive skin reactions. Although migraine is mostly thought of as a type of headache,

standard texts on neurology list many other forms. The multifarious nature and distribution of migraine and allergy suggest a common physiologic morbidity.

Induced hypoglycemia is antispasmodic and antagonistic to sympathetic activity. It is probable that this action relieves the headache. An injection of insulin first excites adrenosympathetic activity to be succeeded in most instances by dominance of the parasympathetic. The phase of adrenosympathetic excitement is often only barely perceptible and passes quickly, but the activity may last for a considerable period. It is the uncomfortable phase for patients, marked by an increased pulse rate, palpitation and vague anxiety. However, even this reaction, after termination by the administration of glucose, is followed by relaxation and a feeling of well being. This appears to be due to a better balanced tension in the vegetative nervous system essential to normal physiologic activity. By means of an insulin injection the writer has repeatedly relieved patients from asthmatic attacks, urticaria and premenstrual cramps. All of these are more or less conditioned by a dysfunction of the sympathetic nervous system.

It should now be understandable why some cases would benefit from organotherapy, others from sympatheticomimetic or vagomimetic drugs, and others from allergic treatment. But most revealing is the general agreement that all patients benefit from psychotherapy. It would be presumptuous to claim hypoglycemic therapy as a panacea for the many ills due to neurocirculatory instability or the many forms of allergic reactions. It can only be claimed that it favorably influences the functioning of the vegetative nervous system on which depends the normal physiology of the human organism.

Summary and Conclusions

Two migrainous patients addicted to opiates were treated with hypoglycemic reactions for the alleviation of withdrawal symptoms. Insulin injections promptly and fully aborted their migraine attacks which occurred during their hospitalization. The rationale for this treatment and its applicability to migraine and allied conditions were discussed.

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THE PARENTERAL USE OF SODIUM LACTATE SOLUTION IN THE PREVENTION OF RENAL COMPLICATIONS FROM PARENTERALLY ADMINISTERED SODIUM SULFADIAZINE*

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Recent studies in this hospital [1] and in other clinics [2] have demonstrated the effectiveness of adjuvant alkali therapy in preventing renal complications from sulfadiazine. This protective action is attributable to the fact that alkalinization of the urine increases the solubility of sulfadiazine and its N^4-acetyl derivative [1, 3, 4] and thereby prevents their precipitation in the kidneys and urinary tract.

The optimal dosage and mode of administration of alkali during oral therapy with sulfadiazine have been studied in a large series of patients.[1] Alkalinization of the urine during parenteral therapy with sodium sulfadiazine presents a special problem which is the subject of this communication.

Material and Methods of Study

Sodium lactate was administered parenterally to approximately 100 postoperative adult patients receiving sodium sulfadiazine parenterally as prophylactic therapy before and after gastric or intestinal resections for ulcer or carcinoma or in the treatment of abdominal abscess or peritonitis. In some patients 2 to 4 gm. of sulfanilamide were dusted into the peritoneal cavity and wound at the time of operation. During the period of study all medications and fluids, with the exception in some instances of small amounts of water, were administered parenterally. The period of postoperative treatment with sodium lactate and sodium sulfadiazine averaged about five days. The preoperative and immediately postoperative sulfadiazine and alkali dosages were variable, as discussed later; from the second postoperative day on, the daily dosage of sodium sulfadiazine and of M/6 sodium lactate solution were, with rare exceptions, 5.0 gm. and 1,100 c.c.† respectively, each divided in two daily doses. The total fluid intake was from 3,000 to 4,000 c.c. daily, and the daily urine volume was usually from 1,500 to 2,500 c.c. In the majority of instances the contents of a 10 c.c. vial of 25 per cent solution of sodium sulfadiazine were added to an infusion bottle of 550 c.c. of

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† Eleven hundred c.c. were chosen since the contents of the infusion bottles of the prepared solutions used were 550 c.c. each.

M/6 sodium lactate at the bedside,* and the mixture was administered intravenously over a period of approximately 40 minutes. In a few instances the mixture of sodium sulfadiazine and sodium lactate solution was administered by clysis; in other instances the sodium lactate solution was injected first, followed by an intravenous injection of 50 c.c. of 5 per cent solution of sodium sulfadiazine. The lactate and sulfadiazine therapy was usually immediately preceded by or followed by injections of glucose or saline solutions.

Special studies were made on 280 urine specimens from 32 of the patients receiving sodium lactate and sodium sulfadiazine parenterally. The urines were collected as separate specimens and preserved at room temperature in bottles containing a layer of toluol until the time of examination; the urinary specimens voided during the evening and night were examined in the morning, and those voided during the day were examined in the late afternoon. Studies were made of the volume, specific gravity, pH, albumin, sulfadiazine and acetylsulfadiazine concentrations, and of the sediment after centrifuging for the presence of crystals of sulfadiazine or acetylsulfadiazine or of red blood cells.

The pH values of approximately one-quarter of the urinary specimens were measured on the Beckman glass-electrode pH meter within a few minutes to a few hours after they were voided. The pH values of the remaining specimens were estimated with nitrazine paper.

The sulfadiazine and acetylsulfadiazine concentrations of the urine and of blood or plasma were measured by the method of Bratton and Marshall,[5] using a Klett-Summerson photoelectric colorimeter. In some instances the blood sulfadiazine concentration was measured by a micro method adapted for 0.05 c.c. blood samples from the Bratton and Marshall [5] macro method.

Blood for measurement of CO_2 content was drawn without stasis from the antecubital vein into an oiled syringe and transferred under oil to a tube containing dry oxalate mixture. The tube was almost filled with blood so that after inserting and plugging a one-hole rubber stopper the blood was covered only by a very thin film of oil. The blood was centrifuged for five minutes at 2,500 R.P.M., the stopper removed, the tube filled with oil and the analysis started immediately. Analyses were made on each sample in duplicate by the method of Van Slyke and Neill [6] using the closed manometric apparatus.

* Sterile M/6 sodium lactate solution in infusion bottles ("Saftiflasks") containing 550 c.c. was supplied to us by Cutter Laboratories; sterile 10 c.c. ampoules of 25 per cent sodium sulfadiazine in water were supplied by Lederle Laboratories, Inc. The pH values of the samples of Cutter M/6 sodium lactate solution which we have tested were approximately 7.2; on addition of the 10 c.c. of 25 per cent sodium sulfadiazine, which has a pH of approximately 9.8, the final pH of the sodium lactate solution was approximately 8.2. No precipitation of sulfadiazine was observed after mixing the two solutions in these proportions. (If the pH of the mixture is lowered below approximately 7.8 by the addition of acid, sulfadiazine precipitates in accord with its solubility characteristics.[4]) The sodium sulfadiazine itself has an insignificant alkalinizing effect in the body, since the sodium content of 5 gm. of the drug is only 0.42 gm. (equivalent to only 1.5 gm. of sodium bicarbonate) and since the sulfadiazine is not oxidized to CO_2 and H_2O but retains its weak acid effect.

RESULTS

Comparison of Incidence of Crystalluria and of Renal Complications from Intravenous Sodium Sulfadiazine with and without Adjuvant Intravenous Sodium Lactate Therapy. Previous studies in this hospital [1, 7] on the incidence of crystalluria and renal reactions in patients receiving sodium sulfadiazine intravenously without adjuvant alkali therapy afford the basis of control for comparison of the findings in the present study in which adjuvant sodium lactate was used. In the previous study of 61 urine specimens from postoperative surgical cases receiving daily a total of 5 gm. of sodium sulfadiazine and no adjuvant alkali therapy, 95 per cent of the urines were acid and the incidence of crystalluria in the acid urines was 43 per cent.[1] Further, 7.4 per cent of 244 patients who received one or more doses of 2.5 gm. of sodium sulfadiazine intravenously and no adjuvant alkali therapy developed some evidences of renal complications.[7]

Of the 280 urine specimens examined in the present study of 32 postoperative patients who received intravenously 5 gm. of sodium sulfadiazine daily, 262 were alkaline as a result of adequate sodium lactate therapy. Of these 262 alkaline urine specimens, only 2 per cent (i.e., five specimens) contained crystals; these five specimens were obtained on the second post-

TABLE I

The Incidences in Acid and Alkaline Urines of Crystalluria from 5 gm. Daily of Sodium Sulfadiazine Intravenously *

Urine Reaction	Number of Specimens Examined	Per Cent of Urines with Sulfadiazine or Acetylsulfadiazine Crystals
Acid	76	56
Alkaline	265†	2

* Combined data of this and a previously reported study [1] in this hospital.

† Two hundred and sixty-two of these alkaline urine specimens were obtained from patients receiving M/6 sodium lactate solution intravenously during therapy with sodium sulfadiazine.

operative day from one patient who had voided acid urines containing crystals during the first postoperative day. There were 18 acid (pH 5.0 to 6.8) urine specimens voided early in the postoperative course by eight patients who were receiving no or too small amounts of sodium lactate during this period. Sixteen of these 18 acid specimens (from seven of the eight patients) contained crystals of sulfadiazine or acetylsulfadiazine. When the urines of these patients were subsequently rendered alkaline with adequate sodium lactate therapy crystalluria disappeared, usually promptly. The pH values of the alkaline urine specimens varied from 7.0 to 8.5 * with most values between 7.4 and 8.2. The pH values of the alkaline urines of the individual patients usually varied during the day between these limits. After alkali therapy was discontinued, the urines usually remained alkaline for 24 to 36

* The occasional observation of pH values over 8.2 (the approximate upper limit of physiological urinary pH [8]) is probably due to loss of CO_2 from the urine.

hours. The large difference in the incidence of crystalluria in acid as compared to alkaline urines from patients receiving sodium sulfadiazine parenterally is shown by the data in table 1.

The level of specific gravity of the 262 alkaline urines varied from 1.004 to 1.030 and averaged 1.015, whereas those of the 18 acid specimens ranged from 1.008 to 1.031 and averaged 1.022. None of the 30 alkaline urines of specific gravity 1.022 or higher contained crystals. The sulfadiazine and acetylsulfadiazine concentrations in the acid urines with crystals were not on the average higher than in the alkaline urines without crystals. The maximum concentrations of sulfadiazine and acetylsulfadiazine observed in the acid urines with crystals were 272 and 165 mg. per 100 c.c., respectively. Many alkaline urine specimens with no crystals contained as high or higher concentrations of free and acetylsulfadiazine up to concentrations of 602 and 168 mg. per 100 c.c., respectively.

In six of the seven patients who had acid urines with crystals postoperatively, the crystals were found on analysis by the Bratton and Marshall method [5] to be chiefly free sulfadiazine in three patients, and chiefly acetylsulfadiazine in the other three.

Hematuria, which was observed in four of the seven patients with acid urines and crystalluria, could not be attributed to kidney damage because it occurred during menstruation or following operative procedures on the perineum. Two of the other three patients with acid urines showed rare red blood cells in the urinary sediment and a slight trace to a trace of albumin, which could have been due to the sulfadiazine therapy. Twenty-three of the 24 patients whose urines were alkaline during the entire period of study showed no hematuria; the one patient in this group who did show hematuria was menstruating.

None of the approximately 100 patients who have received adequate sodium lactate therapy together with parenteral sodium sulfadiazine in this hospital to date have shown clinical evidences of renal complications.

Effect of Sodium Lactate Injections on the Plasma CO_2 Content. In six studies on five patients the plasma CO_2 contents of venous blood, drawn 12 to 18 hours following a dose of 550 c.c. of M/6 sodium lactate and on the second to sixth day of parenteral therapy with 5 gm. of sodium sulfadiazine and 1,100 c.c. of M/6 sodium lactate daily, ranged from 63.6 to 74.5 volumes per cent, the average being 68.9 (table 2). In all of these patients urine specimens, voided shortly before or after the blood samples were drawn for CO_2 measurement, were alkaline. One patient with meningitis, who weighed only 44.6 kilograms (table 2, case 10) and who had received 2,000 c.c. of M/6 lactate solution during the 24 hours preceding the study, had a plasma CO_2 content of 77.7 volumes per cent and alkaline urines. In case 8 only 550 c.c. of sodium lactate had been administered daily for the four days previous to the study; the plasma CO_2 value on the sixth day of therapy was 68.6 volumes per cent but a urine voided at this time was acid

TABLE II

Effect of the Intravenous Injection of 550 c.c. of M/6 Sodium Lactate Solution on the Plasma CO_2 Content of Postoperative Surgical Patients

Experiment No.	Patient	Body Weight	Day of Lactate Therapy*	Urine Reaction before Injection	Plasma CO_2 Content			
					Before Injection	End of Injection	One Hour After	4 Hours After
		kilos			vols. %	vols. %	vols. %	vols. %
1	Rob.	50.6	1st*	—	59.0	63.1	63.7	—
2	Zam.	73.5	4th	Alkaline	67.6	68.3	69.3	69.3
3	Wot. (11/16)	88.6	3d	Alkaline	69.5	—	72.6	—
4	Wot. (11/19)	88.6	6th	Alkaline	66.6	68.7	68.5	—
5	Koh.	61.5	3d	Alkaline	—	70.0	72.0	70.7
6	Cur.	58.2	3d	Alkaline	74.5	75.3	—	—
7	Ril.	74.0	4th	Alkaline	63.6	70.8	67.5	63.4
8	Man.	94.9	5th*	Acid	68.6	76.2	78.1	—
9	Vet.	40.5	2d	Alkaline	71.7	73.8	77.4	78.7
10	McK.	44.6	2d*	Alkaline	77.7†	82.3†	80.9†	—

* Daily injections of a total of 1,100 c.c. of M/6 sodium lactate solution and 5 gm. of sodium sulfadiazine, except in case 1 studied a few hours postoperatively, case 8 which had received only 550 c.c. of M/6 lactate daily, and case 10, a patient with meningococcus meningitis who had received 2,000 c.c. of M/6 lactate and 12 gm. of sodium sulfadiazine in the previous 24 hours.

† 350 c.c. of M/6 lactate in this injection.

(pH 6.2) and contained acetylsulfadiazine crystals. The plasma CO_2 content a few hours postoperatively in a patient (case 1) who had received 18 gm. of sodium bicarbonate daily with 6 gm. of sulfadiazine for one and one-half days preoperatively was 59.0 volumes per cent.

Following the intravenous injection of 550 c.c. of M/6 lactate solution (from 5.8 to 13.6 c.c./kilo of body weight), the CO_2 content of the plasma invariably increased to a slight extent (table 2). The highest values were usually observed at the end of, or one hour after the end of, the injection which consumed approximately 40 minutes. The CO_2 values decreased slowly, usually being somewhat higher four hours after the end of injection than before. The extent of increase in CO_2 content of plasma to be expected from the intravenous injection of 550 c.c. of M/6 sodium lactate solution may be calculated approximately, in accord with considerations outlined by Hartmann [9] from the formula:

$$\frac{2.24 \times \frac{550}{6}}{\text{Body weight (kilos)} \times 0.67}, \text{ i.e., } \frac{205}{\text{Body weight (kilos)} \times 0.67}, \text{ or } \frac{306}{\text{body weight (kilos)}}$$

The maximum increases in plasma CO_2 content observed in our studies accord with the calculated increases within reasonable expectation (table 3);

the averages of the observed and calculated increases are 5.0 and 4.6 volumes per cent, respectively (table 3).

The Appropriate Dosage of Parenterally Administered Sodium Lactate. The volume of M/6 sodium lactate solution required to render the urine alkaline postoperatively is very variable, depending upon the degree of dehydration and acidosis present and the amount of alkali therapy which has been administered preoperatively or during operation. In instances where the surgical procedure has not been very extensive or prolonged, preoperative therapy with 550 c.c. of M/6 sodium lactate containing 2.5 gm. of sodium

TABLE III

Comparison of Observed and Calculated Increases in Plasma CO_2 Content Following the Intravenous Injection of 550 c.c. of M/6 Sodium Lactate Solution

Experiment No.	Patient	Body Weight	Dose of M/6 Sodium Lactate	Plasma CO_2 Content			Increase in Plasma CO_2 Content	
				Before Injection	Highest CO_2 Value after Injection			
					Time after Injection	Value	Found	Calculated
		kilos	c.c./kilo	vols. %	hours	vols. %	vols. %	vols. %
1	Rob.	50.6	10.9	59.0	1	63.7	4.7	6.1
2	Zam.	73.5	7.5	67.6	1	69.3	1.7	4.2
3	Wot. (11/16)	88.6	6.2	69.5	1	72.6	3.1	3.5
4	Wot. (11/19)	88.6	6.2	66.6	End of injection	68.7	2.1	3.5
7	Ril.	74.0	7.4	63.6	End of injection	70.8	7.2	4.1
8	Man.	94.4	5.8	68.6	1	78.1	9.5	3.3
9	Vet.	40.5	13.6	71.7	4	78.7	7.0	7.6
10	McK.	44.6	7.8*	77.7	End of injection	82.3	4.6	4.4
						Average.....	5.0	4.6

* Only 350 c.c. of M/6 sodium lactate administered.

sulfadiazine followed by similar medication within a few hours postoperatively has been sufficient to maintain the postoperative urines alkaline, and prevent crystalluria from the sodium sulfadiazine. If no alkali therapy was given a short time preoperatively or during the operation, acid urines with crystalluria were not infrequently observed following an initial postoperative injection of 2.5 gm. of sodium sulfadiazine with 550 c.c. of M/6 sodium lactate solution. After extensive surgical procedures of several hours' duration an initial postoperative injection of 1,000 c.c. or more of M/6 sodium lactate solution has usually been required to render the urine alkaline. This has been true even when the preoperative urines have been alkaline due to the ingestion of Sippy tablets or sodium bicarbonate with sulfadiazine or after a preoperative injection of 2.5 gm. of sodium sulfadiazine in 550 c.c. of M/6 sodium lactate.

A total daily dose of 1,100 c.c. of M/6 sodium lactate together with 5 gm. of sodium sulfadiazine, each divided into two doses administered every 12 hours, was sufficient to maintain the urine alkaline during the later post-operative days of the 32 patients studied extensively.

TABLE IV

Increases in Whole Blood and Plasma Sulfadiazine Concentration Immediately after the Intravenous Injection of 2.5 Gm. of Sodium Sulfadiazine in 550 c.c. of M/6 Sodium Lactate

Patient	Time for Injection	Specimen Examined	Sulfadiazine Concentration Before Injection	Sulfadiazine Concentration After Injection	
				0–5 Minutes	30–60 Minutes
	minutes		mg./100 c.c.	mg./100 c.c.	mg./100 c.c.
2.5 gm. Sodium Sulfadiazine Administered in 550 c.c. M/6 Sodium Lactate (i.e., 0.5% solution)					
Fia	40	Whole Blood	5.8	16.8	13.9
McC. 9/12	43	Whole Blood	3.6	—	9.0
McC. 9/12	40	Whole Blood	5.8	—	10.3
McC. 9/13	40	Whole Blood	2.4	—	7.3
McC. 9/13	60	Whole Blood	2.4	8.0	—
Bog	40	Whole Blood	—	9.8	8.6
Mof	60	Whole Blood	—	12.5	11.4
Spe	60	Whole Blood	5.9	—	10.3
Koh	40	Whole Blood	—	15.2	13.6
Lor	75	Whole Blood	5.9	10.0	—
Jac	40	Whole Blood	1.8	10.4	7.5
Bar	40	Whole Blood	3.8	10.9	9.4
Sch	60	Whole Blood	1.8	10.5	7.8
Ste	30	Whole Blood	5.9	15.1	12.1
Man	40	Plasma	2.2	10.5	8.0
McK	30	Plasma	5.4*	13.9*	12.3*
Wot	40	Plasma	4.0	9.8	7.7
Vet	40	Plasma	11.2	21.2	18.6
Rin	55	Plasma	2.6	12.1	8.7
2.5 gm. Sodium Sulfadiazine Administered in 50 c.c. of Water (i.e., 5% solution)					
Tay	4	Whole Blood	10.8	33.0†	—
Cap	1′ 32″	Whole Blood	1.4	34.6†	10.0
Zam	3	Plasma	2.0	31.2†	8.9

* Only 350 c.c. of solution containing 1.6 gm. of sodium sulfadiazine administered.

† Equilibrium distribution obviously not attained at end of injection (0–1 minute after) of the concentrated solution of sodium sulfadiazine.

Sulfadiazine Concentrations in the Blood Following Infusions of 0.5 Per Cent Sodium Sulfadiazine in M/6 Sodium Lactate Solution. The concentration of sulfadiazine in the blood or plasma at intervals following the intravenous infusion of 2.5 gm. of sodium sulfadiazine in 0.5 per cent solution in M/6 sodium lactate solution in approximately 40 minutes was studied to discover the height to which the blood sulfadiazine concentration rose and the rate of attainment of equilibrium concentration (table 4). It was observed that the blood or plasma sulfadiazine concentration at the end of such injections was 5 to 11 mg. per 100 c.c. higher than before injection,

the amount of increase being roughly inversely proportional to the body weight (table 4). The sulfadiazine concentration fell only 1 to 3 mg. per 100 c.c. during the 30 to 60 minutes following the end of injection, the amount of decrease in this time being in many instances not much greater than could be accounted for by excretion of the drug during the interval (table 4). The data indicate, therefore, that at this rate of administration of sulfadiazine the distribution of the drug throughout the body is so complete as to attain approximate equilibrium during the injection. On the other hand, in several instances in which 2.5 gm. of sodium sulfadiazine dissolved in 50 c.c. of water (i.e., 5 per cent solution) were injected intravenously in a period of two to four minutes, a high peak in the sulfadiazine concentration of the blood was obtained at the end of injection, and the concentrations 30–60 minutes later, when equilibrium distribution throughout the body was presumably reached, were some 20 or more mg. per 100 c.c. lower than at the end of injection (table 4).

The increase in plasma or whole blood sulfadiazine concentration to be expected when equilibrium is reached after intravenous injections of sodium sulfadiazine can be calculated approximately on the basis of data from previous studies of the distribution of sulfadiazine in the body.[10] The formula for this calculation for plasma is based on the relationship between the amount of sodium sulfadiazine administered, the amount of body water of the patient, the percentage water in the plasma, and the ratio of bound to unbound drug in the plasma. This formula is as follows:

$$\text{Expected increase in plasma sulfadiazine concentration (in mg. per 100 c.c.)} = \frac{\text{mg. Na sulfadiazine injected} \times a}{\text{body weight (kilos)} \times b \times c} \times d + \frac{\text{mg. Na sulfadiazine injected} \times a}{\text{body weight (kilos)} \times b \times c} \times d \times e,$$

where a is a factor to convert sodium sulfadiazine to sulfadiazine and is equal to 0.92, b is a factor to convert body weight to body water and is 0.75, c is a factor to convert liters to 100 c.c. units and is 10, d is the ratio of plasma water volume to plasma volume and is 0.94, and e is the ratio of bound to unbound sulfadiazine (in plasma of 7.0 gm. per cent protein) and is equal to 1.27. Substituting these factors in the above equation, the calculated increase in *plasma* sulfadiazine concentration (in mg. per 100 c.c.) after the intravenous injection of 2.5 gm. of sodium sulfadiazine may be simply expressed as $\frac{654}{\text{body weight (kilos)}}$. The increase in whole blood sulfadiazine concentration after this injection can be calculated approximately from the plasma value by multiplying the latter by the factor $\frac{1}{1.4}$, described elsewhere [10, 11, 12];

i.e., the calculated increase in *whole blood* sulfadiazine concentration (in mg. per 100 c.c.) $= \frac{467}{\text{body weight (kilos)}}$.

The increases in plasma and whole blood concentrations of sulfadiazine which were observed immediately after the intravenous injection of 2.5 gm. of sodium sulfadiazine in 0.5 per cent solution in M/6 sodium lactate compare reasonably well with the concentrations to be expected (table 5) as calculated from the above formula; the average observed value for all studies was 8.0 mg. per 100 c.c. compared with the average calculated value of 8.3 mg. per 100 c.c.

TABLE V

Comparison of Observed and Calculated Increases in Whole Blood and Plasma Sulfadiazine Concentrations Immediately After the Intravenous Injection of 2.5 Gm. of Sodium Sulfadiazine in 550 c.c. of M/6 Sodium Lactate Solution

Patient	Body Weight	Fluid Examined	Increase in Sulfadiazine Concentration	
			Observed	Calculated
	kilos		mg./100 c.c.	mg./100 c.c.
Fia.	51.0	Whole Blood	11.0	9.1
McC.	71.5	Whole Blood	5.6	6.5
Lor.	67.5	Whole Blood	4.1	6.9
Jac.	61.1	Whole Blood	8.6	7.6
Bar.	72.0	Whole Blood	7.1	6.5
Sch.	72.7	Whole Blood	8.7	6.4
Ste.	58.5	Whole Blood	9.2	8.0
Man.	94.4	Plasma	8.3	6.9
McK.	44.6	Plasma	8.5*	9.3*
Wot.	88.6	Plasma	5.8	7.4
Vet.	40.5	Plasma	10.0	16.1
Rin.	76.4	Plasma	9.5	8.6
		Total Average	8.0	8.3

* 1.6 gm. of sodium sulfadiazine administered in 350 c.c. of M/6 sodium lactate.

DISCUSSION

Although sulfadiazine is administered most frequently by the oral route there are many instances, especially in surgical practice or in fulminating bacterial infections in which it is necessary or advisable to administer the drug parenterally. In such instances it is also usually necessary that any adjuvant therapy to alkalinize the urine be given parenterally.

The extensive studies of Hartmann et al.[9, 13, 14, 15] have clearly demonstrated the value and safety of parenterally administered sodium lactate solution as a therapeutic agent in correcting acidosis.

The results of the present study in postoperative surgical patients show that M/6 sodium lactate solution administered parenterally also affords a valuable means of alkalinizing the urine during treatment with sodium sulfadiazine parenterally (table 1). It has been the usual practice on the surgical services of this hospital to administer postoperatively to patients in whom

sulfonamide therapy was indicated a total daily dosage of 5.0 gm. of sodium sulfadiazine intravenously divided into two doses administered each 12 hours at the time of administration of other fluids. For purposes of practical therapy it was decided at the outset of the present study to ascertain whether two parenteral injections of M/6 sodium lactate solution 12 hours apart would suffice to maintain adequate alkalinity, prevent crystalluria and avoid alkalosis. The laboratory and clinical studies which are reported above show this to be the case.

Whereas an initial dose of 550 c.c. of M/6 sodium lactate solution (equivalent to 7.7 gm. of sodium bicarbonate) administered parenterally at the onset of therapy is sufficient to render the urine alkaline in patients with no acidosis, initial doses of 1,000 to 1,500 c.c. have been required in patients with acidosis from extensive surgical operations or fulminating acute infections. These dosages are essentially equivalent to those of orally administered sodium bicarbonate previously found by us and by others requisite to render the urine alkaline under these different conditions.[1, 16, 17] Once the urine has been rendered alkaline, a total daily dosage of 1,100 c.c. of M/6 sodium lactate divided into two 12-hour injections has been sufficient to maintain urinary alkalinity (usually pH 7.4 to 8.0) and to prevent crystalluria throughout the 24-hour period. This daily dosage of lactate solution by virtue of oxidation of the lactate ion or its conversion to glycogen [18, 19] has an alkalinizing effect in the body equivalent to approximately 15 gm. of sodium bicarbonate and is, therefore, approximately equivalent to the total oral daily dosage of 15.6 gm. of sodium bicarbonate (2.6 gm. (40 grains) every four hours) which has been used extensively in this hospital [1] to maintain alkalinity when 4 to 6 gm. of sulfadiazine are given daily by mouth.

Theoretically, to ensure the prevention of crystalluria, the urine should be alkalinized before the sodium sulfadiazine is administered. For purposes of practical parenteral therapy, however, it has been the practice here to administer to patients without acidosis an initial injection of 2.5 gm. of sodium sulfadiazine in 550 c.c. of M/6 sodium lactate solution. When this procedure is used, the blood concentration of sulfadiazine does not reach a high level, fluid is afforded for diluting the excreted sulfadiazine and the urine soon turns alkaline, probably before all of the sodium sulfadiazine has been administered. However, in patients with acidosis or potential acidosis sodium lactate solution in sufficient amounts to alkalinize the urine should be given prior to the sodium sulfadiazine therapy. Under certain circumstances, especially in prolonged operations where appreciable fluid loss may occur, it may be advisable to administer sodium lactate solution during operation. In some instances, such as in fulminating meningococcus meningitis in which there may be some acidosis but in which sulfonamide therapy is indicated without delay, it has been routine in this hospital to administer an initial parenteral dose of 5 gm. of sodium sulfadiazine in 1,100 c.c. of M/6 sodium lactate solution, and to study the pH of the urine with nitrazine

paper during the next few hours as a basis for deciding upon subsequent alkali therapy.

Undoubtedly 1,100 c.c. of M/6 sodium lactate solution daily would also be sufficient in most instances to protect against crystalluria from daily amounts of parenterally administered sodium sulfadiazine somewhat larger than used in the present study. Fox and Jensen [2] previously have discussed the problems of protecting against crystalluria and resultant renal complications from massive intravenous doses of sodium sulfadiazine.

In none of the approximately 100 postoperative surgical patients who have received 1,100 c.c. of M/6 sodium lactate solution daily on the surgical services of this hospital have clinical evidences of alkalosis been observed. The plasma CO_2 contents of a series of patients (table 2) receiving these doses of lactate remained, except occasionally during a few hours following a repeated injection, within the limits of accepted normal values,[20, 21] namely 55 to 75 volumes per cent. There appeared to be no cumulative rise in plasma CO_2 concentration as the medication was continued for days (table 2); in fact, no cumulative effect would be expected since the urinary pH was not at the upper limit of the physiological range throughout the day. From the findings of Palmer and Van Slyke [21] it is presumed that the plasma CO_2 contents in these patients even 12 hours after an injection are nevertheless at least some 3 volumes per cent higher than would obtain in the same individuals if the urines were acid. The maximum increases in plasma CO_2 content after a given injection of 550 c.c. of the M/6 lactate solution were observed usually one hour after the end of injection and were not great, averaging 5.0 volumes per cent * (table 3). Hartmann et al.,[15] using larger doses, have shown previously that intravenously injected sodium lactate is completely metabolized in from one to two hours, that the urine becomes alkaline almost immediately after injection, and that the urinary alkalinity is prolonged for many hours. Our findings with small and repeated doses accord with these conclusions.[15] The difficulties and dangers which may be encountered in attempting to alkalinize the urine in patients with nephritis, and the precautions which must be exercised in such instances have been emphasized by Palmer and Van Slyke [21] and Hartmann and Senn.[9, 14]

The total fluid volume administered in these patients was usually 3,000 to 4,000 c.c. daily, consisting of approximately 2,000 c.c. of 5 per cent glucose, 1,000 c.c. of M/6 sodium lactate,† and 500 c.c. of isotonic sodium

* If the values are omitted for case 8 (table 3), in which the maximum increase in CO_2 content was exceptionally high, the averages for all other cases are 4.3 and 4.8 volumes per cent for the observed and calculated increases, respectively. When this observed average of 4.3 is corrected to represent the concentration in the water of the plasma, the value becomes 4.6 as compared with the calculated average increase in the body water of 4.8 volumes per cent. These findings indicate that only a small amount of the lactate ion itself and only a small amount of sodium bicarbonate formed from the lactate is excreted in the urine during the period from the beginning of the injection to the time when the plasma CO_2 value becomes maximum.[15]

† It is of interest to note that 1,000 c.c. of M/6 sodium lactate solution has a calculated caloric value of 54 calories compared with approximately 200 calories for 1,000 c.c. of 5 per cent glucose solution.

chloride solution. It is to be noted that the daily urinary volume of these patients was usually between 1,500 and 2,500 c.c., and that alkali therapy is advocated together with optimal fluid administration as a necessary additional protective measure against renal complications.

The intravenous route of parenteral administration of the lactate solution and of the sodium sulfadiazine (in 0.5 solution) has been used in most of the studies of this report. In some patients, as in small children or in adults in whom difficulty is encountered in administration of solutions by the intravenous route, the administration of the sodium salts of the sulfonamides by the subcutaneous route may be more practicable. Taplin et al.[22] and Hartmann [23] have concluded that the sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine may be administered subcutaneously in concentrations of 0.4 to 0.8 per cent in lactate Ringer's, isotonic sodium chloride, or M/6 sodium lactate solutions. Taplin et al.[22] have reported that in adults the blood concentrations of the sulfonamides after hypodermoclysis vary greatly owing to variation in the rate of absorption, and that treatment by this route must be based on the results of repeated blood analyses in each individual.

In our studies it was found that the increase in sulfadiazine concentration of the blood obtained in a given individual at the end of an intravenous injection of 2.5 gm. of sodium sulfadiazine in 0.5 per cent solution in M/6 sodium lactate approximated that which would be expected by calculation from the formula: $\frac{467}{\text{Body weight (kilos)}} =$ increase in blood sulfadiazine concentration (mg. per 100 c.c.),* a formula derived from earlier studies of the distribution of this drug in the body [10] (also see Results). The rate of excretion of the drug is, of course, somewhat variable in different individuals or even in the same individual under different conditions of fluid therapy. Published data [24] and observations we have made, however, show that the blood concentration of sulfadiazine usually drops about 60 to 70 per cent in 12 hours after an intravenous injection of the drug in patients with normal kidneys and daily urinary volumes of 1,000 to 2,000 c.c. One can predict, then, with a fair degree of accuracy what the blood level will be after an intravenous injection of a given amount of sodium sulfadiazine and how much it will decrease during a given time interval. Although such calculations are helpful as a guide, it is nevertheless important, because of variations in excretion of the drug and tendency toward a cumulative effect, that blood analyses be made at appropriate intervals in relation to the sodium sulfadiazine dosage to ascertain whether the limits of variation are within those desired in a given individual. It is to be pointed out that a "blood level" of sulfadiazine in the sense that a rather constant concentration exists during oral sulfadiazine administration does not exist when sodium sulfa-

* This formula applies only when equilibrium distribution is attained; one therefore may use it also to estimate the increase in blood concentration at equilibrium (approximately 30 minutes) after injection of concentrated solution (5 per cent) of sodium sulfadiazine, but not immediately after (table 4).

diazine is given parenterally at intervals; with intravenous therapy the blood concentration of sulfonamide is obviously at its highest at the end of an injection and at a low point at the end of the interval between injections.

The routines of administration of sodium bicarbonate orally or of sodium lactate solution parenterally, which we have advocated on the basis of the previous [1] and present studies with sulfadiazine, would presumably be applicable in protecting against renal damage from certain other sulfonamide drugs, although the degree of protection can be stated only after wide clinical trial with these other drugs. To a greater or less extent than with sulfadiazine, crystalluria and renal complications occur during therapy with sulfapyridine,[25] sulfathiazole,[25] sulfamerazine,[26, 27] sulfamethazine [28] and sulfapyrazine.[29] Since the solubilities of sulfapyridine and its N^4-acetyl derivative [30] remain the same throughout the physiological range of urinary pH, there is no known theoretical basis to suggest that alkalinization of the urine would protect against renal complications from this drug, and in fact it has been common clinical experience that it does not. On the other hand, from the higher solubilities of all the other above-mentioned drugs and their N^4-acetyl derivatives in the alkaline range of urinary pH [31, 32, 33] in comparison with those in the acid range, one might expect that alkalinization of the urine would be of value, perhaps more with sulfamerazine, sulfapyrazine and sulfamethazine than with sulfathiazole, and adjuvant alkali therapy has been advocated with all of these drugs.[26, 27, 28, 32, 33, 34]

Summary and Conclusions

1. A study of the findings in approximately 100 patients, chiefly postoperative surgical cases, shows that alkalinization of the urine with M/6 sodium lactate solution administered parenterally prevents crystalluria and renal complications consequent to crystalluria during therapy with the usual doses of parenterally administered sodium sulfadiazine.

2. The initial dose of sodium lactate required to alkalinize the urine at the onset of therapy with sodium sulfadiazine depends upon the degree of acidosis present and varies usually from 500 to 1,500 c.c. of M/6 sodium lactate solution in adults with normal kidney function.

3. Thereafter, 1,100 c.c. of M/6 sodium lactate solution daily, divided into two doses administered every 12 hours to adult patients receiving sodium sulfadiazine, is usually appropriate to maintain the urine alkaline and prevent crystalluria from the sulfadiazine.

4. The plasma carbon dioxide content is not greatly affected by this dosage of lactate solution. No evidences of clinical alkalosis have been observed in our series of patients. It is pointed out that caution must be exercised to prevent alkalosis when attempting to alkalinize the urine of patients with nephritis.

5. From the results of studies of the sulfadiazine concentration of the blood following intravenous injections of sodium sulfadiazine, it is advocated

that the drug be administered in the relatively low concentration of 0.5 per cent in M/6 sodium lactate solution, or certain other parenterally utilizable isotonic solutions rather than in 5 per cent solution in water.

6. It is suggested that parenteral sodium lactate therapy as prescribed here would similarly be of value in protecting against renal complications from parenteral administration of certain other sulfonamide drugs.

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THE TREATMENT OF MENINGOCOCCUS INFECTIONS WITH ESPECIAL REFERENCE TO THE WATERHOUSE–FRIDERICHSEN SYNDROME*

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In a Naval Hospital situated at one of the large training stations we had an opportunity to observe during the winter and spring a relatively large number of meningococcus infections.

Meningococcus infections characteristically increase in number in time of war. Conditions at large training stations, where men live in barracks and where new recruits are constantly arriving, are ideal for the production of a state of affairs where these infections are endemic. The new recruits are housed in barracks, each containing 112 men on the lower and another 112 on the upper floor. These men sleep in double-decker bunks. Ventilation is good.

We were very much surprised to find that there was no tendency for the epidemic to spread within a single barracks. The largest number of cases occurring in one company within a period of a month was four. The regiments varied in number of cases, two having 38 and 33 respectively, whereas the rest had smaller numbers. One got the impression that there probably existed a reservoir of meningococci carried by healthy men, and that as they became exposed a certain number of susceptible individuals developed the disease. No cases occurred among the officers or among the staff of the hospital. We had no cross infections in the hospital where rigid isolation (gown and mask) technic was employed.

In view of the difficulties encountered in growing meningococci from the nasopharynx, even in patients who had actual meningitis, no routine cultures of healthy recruits were made to try to determine the carrier rate. No attempts were made to control the epidemic. The failure of further occupants of a given barracks to develop the disease after two or three cases had appeared among them made us believe that such measures as taking a whole company out of all physical activity or the prophylactic use of the sulfonamides were not justified under the conditions we encountered. The number of susceptible individuals must have been small, if in a station of this size only 132 men developed a disease that was spread from endemic foci all over the station.

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Although in most instances our methods of controlling the endemicity of meningococcus infections have not improved, the lowering of the mortality from and of the complications of cerebrospinal fever through the use of the sulfonamides has been one of the most brilliant achievements of this type of chemotherapy.

It is our purpose in this paper to discuss the results of therapy in (1) 76 cases of meningococcus meningitis, (2) 50 cases of meningococcemia without meningitis, and (3) 6 cases of the Waterhouse-Friderichsen syndrome.

Part I

From the time of the opening of the hospital in February until August first, 76 cases of meningococcus meningitis were admitted. All of these patients presented the characteristic clinical picture of the disease. Purulent spinal fluid was obtained in all. Hemorrhagic rashes were present on admission in all but six cases seen. The meningococcus was either found on examination of the spinal fluid smear or cultured from the spinal fluid, or both, in 45, or 59 per cent, of the cases.

All of our patients were treated with sulfadiazine. On admission the average patient received 5 gm. of sulfadiazine and from 1,000 to 1,500 c.c. of saline intravenously. Each patient received from the onset a minimum fluid intake of 3,000 c.c. daily. Until the patient could take this amount of fluid by mouth the deficit was made up by intravenous administration. In severe cases another 5 gm. of sulfadiazine were not infrequently given intravenously at the end of four hours if the drug could not be taken orally. However, the average patient after the initial dose received 2 to 2.5 gm. every four hours, the oral route being substituted as soon as he was able to take fluids by mouth. This rather large initial dosage produced high blood levels of the drug, the average concentration attained being about 15 mg. per 100 c.c. Alkalies were regularly administered and careful attention was paid to the maintenance of adequate fluid intake and output. Ten patients had gross hematuria. When this complication appeared, sulfanilamide was substituted for sulfadiazine and proved entirely satisfactory. Subsequent sulfonamide dosage was guided by the estimation of the blood concentration. In general, levels of 10 to 15 mg. per 100 c.c. were maintained until the temperature had returned to normal, and then levels of 5 to 10 mg. were maintained for about a week.

A few [12] of our earlier cases received meningococcus antitoxin. We could not see that the patients receiving this preparation did better in any way than those not receiving it; therefore, its use was discontinued, as in most patients it caused severe late serum sickness. Lumbar puncture was done for diagnostic purposes, enough spinal fluid being withdrawn to reduce the pressure to normal. In eight cases a second puncture was done from one to three days after the initial puncture. In these cases the persistence of

headache and stiff neck and the failure of the patient to make the usual rapid return to a satisfactory state of consciousness made it seem likely that further reduction of cerebrospinal fluid pressure would be helpful. In each case an increased pressure was found at the time the repeat tap was done. All of the patients recovered. Two (1.5 per cent) had residual nerve deafness. Otherwise, there were no complications.

Part II

Fifty of our cases are classified as meningococcemia because they never developed the symptoms and signs of meningitis. In the few of these cases in which spinal puncture was done, the findings were either normal or else abnormal only to the extent of a slight pleocytosis. Most of these patients were probably simply in the bacteriemic (premeningitic) phase of cerebrospinal fever and would have developed meningitis had not treatment been promptly instituted. However, there were some who over a course of one to several days had had symptoms of a bacteriemia without evidence of invasion of the nervous system. The latter group had the characteristic rash, usually enlargement of the spleen, usually fever, malaise, muscular stiffness, particularly of the lower extremities, and polyarthralgia, and not infrequently monarticular arthritis with accumulation of fluid within the joint capsule. No joint punctures were done. All swollen joints responded to sulfonamide therapy.

The rashes were of two types: (1) the usual fine hemorrhagic rash with petechiae on the extremities and trunk varying in size from a pin point to 2 or 3 mm., and (2) an erythematous rash with maculopapular lesions varying in size from 0.5 to 2 cm. fading on pressure at first, but later developing fine hemorrhagic centers in many of the lesions. The fully developed lesion closely resembled a flea bite.

The meningococcus was recovered from the blood in a relatively small number of these cases (seven, or 15 per cent, of 46 cases cultured) and from the nasopharynx in only five cases (10 per cent). Both types of rash were so often associated with the development of meningitis, were so typical in their appearance and responded so promptly to therapy that we are quite certain of the fact that all the cases reported as such had meningococcemia.

During the early period a few cases were treated orally, but our experience proved that it was better to raise the blood level quickly by giving the initial dose of sulfadiazine intravenously. Some of the cases treated orally developed meningitis before the response to chemotherapy took place. When in the absence of meningeal signs intravenous therapy was used, meningitis rarely developed. The same large doses were used as were described above in connection with the treatment of meningitis, and the same precautions were taken to avoid the hazards incident to such dosage. All recovered uneventfully.

Part III

The Waterhouse-Friderichsen syndrome has been the subject of many reports in the current literature. Voelcker [1] in 1894 was the first to describe a case of fulminating illness with purpuric eruption and bilateral adrenal hemorrhage. A number of reports of similar cases appeared in the English literature until 1901, when Graham-Little [2] described 11 cases and established the condition as a clinical entity.

The characteristic clinical features mentioned in most descriptions are a fulminating course suggesting an acute sepsis, often ushered in by symptoms such as headache and vomiting, usually with the development of high temperature and a widespread purpuric rash, and running a rapidly fatal course characterized by cyanosis, hyperpnea, and the signs of circulatory failure.

Pathologically the outstanding feature has been hemorrhage into one or both suprarenal glands. However, Williams [3] has recently reported a series of 17 fatal cases clinically indistinguishable in which only nine had adrenal hemorrhage. Banks and McCartney [4, 5] separate from the others a group in which there are parenchymatous changes in the central nervous system consisting of congestion and edema with capillary thrombosis followed later by inflammatory perivascular infiltration of polymorphonuclear leukocytes around the vessels. It has been noted by others that some patients retain consciousness until the end, whereas others succumb after a period of deep coma. Banks and McCartney believe that it is in the comatose cases that these parenchymatous lesions are most often found.

Waterhouse [6] reported a case in 1911 and Friderichsen [7] in 1918 reported another case. Both reviewed the literature; Friderichsen found in blood culture a small gram-negative diplococcus but did not identify it as a meningococcus. MacLagan and Cooke [15] in 1916 were the first to connect the syndrome with the meningococcus. Although other organisms have been incriminated, the meningococcus has been found more and more frequently to be the causative agent. Between MacLagan and Cooke's paper and 1937 when Sacks [9] reviewed the status of this syndrome, 21 cases were reported in which statements as to the causative agent were made, and in 60 per cent of them the presence of the meningococcus was demonstrated.

Meningococci were first demonstrated in smears from the purpuric lesions in the skin by Netter and Salanier.[10] McLean and Caffey [11] were able to find meningococci by direct smear in the purpuric lesions of 83 per cent of 18 cases of meningococcemia. Andrewes,[12] in 1906, was able to demonstrate the meningococcus in blood films. In 1936 Hall [13] demonstrated the organisms in the direct blood smear in a fulminating case of meningococcemia. Chief Pharmacist Murphy, then working in the laboratory on the *Relief*, was the first to call Hall's attention to the peculiar appearance of the leukocytes in the blood smear, and it was he, in our laboratory, who first demonstrated them to us.

For many years the syndrome was considered uniformly fatal. However, Magnusson [8] in 1934 stated that he had seen a recovered case, although he did not give the details. Grace, Harrison, and Davie [14] reported in some detail three fatal cases and mentioned a woman of 40 who with sulfonamide and adrenal substitution therapy got well.

Sharkey [16] encountered the Waterhouse-Friderichsen syndrome in a young woman who was in the eighth month of pregnancy. Although the blood culture was negative, the serum gave a positive complement fixation reaction

FIG. 1. Purpuric eruption in case of Waterhouse-Friderichsen syndrome.

with the meningococcus. The serum sodium was approximately 127 meq./L. This patient was treated with adrenal cortex substance, saline, and sulfapyridine. She recovered in spite of a premature delivery (stillbirth) and the development under treatment of meningitis with purulent spinal fluid.

Other recovered cases have been described by Carey,[17] Bickel,[18] and Rucks and Hobson.[19] Three of Banks and McCartney's [4] cases recovered. Carey's patient had a serum sodium of 147.7 meq./L.

Our patients whom we have classified as belonging to the Waterhouse-Friderichsen group had rashes that were truly purpuric (figure 1). Unlike the patients with uncomplicated meningococcemia there were usually con-

junctival hemorrhages which were sometimes so marked that the patients had "bloody tears." Cyanosis was usually marked and even fresh purpuric areas took on a deep purple hue. As noted by Banks and McCartney, these patients might be either unconscious or quite alert. The blood pressure was always low; the radial pulse was soft and barely perceptible. In two cases it was unobtainable for several hours before death. There was collapse of the peripheral veins, making intravenous administration of fluids difficult. Sometimes it was possible to recognize the hemorrhagic state likely to result in damage to the suprarenal glands before evidences of such damage appeared; but more often the symptoms and signs of possible adrenal insufficiency appeared as the rash was coming out and the development of the circulatory collapse was often extremely rapid. We have had the unusual opportunity of seeing six cases who presented the characteristic findings of this condition.

We have not included four other cases which we consider borderline. All of these four had purpuric rashes of varying degree, hypotension, and weak, thready pulse; three had conjunctival hemorrhage. They were treated in the same manner as those with the full-blown Waterhouse-Friderichsen syndrome that recovered. Therapy was started very early in the course. Response to therapy was rapid. They were quantitatively less severe. Their ability to maintain circulatory compensation without continued adrenal substitution therapy after the initial administration of adrenal cortical substance makes it doubtful that they had suprarenal damage. They are, therefore, included among the cases of meningococcemia.

The following is the case history of one of our two cases of the Waterhouse-Friderichsen type of meningococcemia who recovered.

Case Report

C. R. The patient was admitted about 2 p.m. on April 6 in coma. No history could be obtained. His temperature was 104° F. He was cyanotic. There were scattered purpuric areas on the skin and a petechial rash over the whole body, especially on the trunk and lower extremities. His neck was stiff, but the Kernig was negative. He was only slightly hyperpneic. The lungs were clear. The heart sounds were of poor quality with a rate of 126; his pulse was rapid, weak and thready, difficult to palpate at the wrist. His blood pressure was 80 mm. Hg systolic and 60 mm. diastolic. Examination of the abdomen was negative.

Laboratory Studies: urine, straw colored, clear; specific gravity 1.010; alkaline: albumin and glucose negative; microscopic, occasional hyaline casts. White blood cells 6–8 per high power field. Hemoglobin 14 gm.; red blood cells 5,390,000; white blood cells 18,900; polymorphonuclears 92 (16 band forms); lymphocytes 7; juvenile neutrophiles 1. Bleeding time 2 minutes 40 seconds. Clotting time 4½ minutes. Platelets 291,000. Blood type A.

Spinal Puncture: fluid clear; 2 cells per cu. mm.; globulin negative. Sugar 100 mg./100 c.c. Culture negative.

Blood Culture: not obtained, because of a delay in getting the culture materials and the decision to give sulfadiazine at once in view of the patient's condition.

Immediate Therapy: 20 c.c. adrenal cortex extract intravenously; 5 gm. sodium sulfadiazine in 100 c.c. saline intravenously; 10,000 units meningococcus antitoxin

intravenously; 10,000 units meningococcus antitoxin intramuscularly; 10 mg. desoxycorticosterone intramuscularly; 10 c.c. adrenal cortex extract intravenously; continuous infusion 5 per cent dextrose in saline; 250 c.c. of whole blood.

The infusion was stopped at about 7 p.m. as he was taking fluids by mouth. Sulfadiazine was given by mouth after the initial intravenous dose at the rate of 2 gm. every four hours.

The blood pressure was 100 mm. Hg systolic and 40 mm. diastolic at 4:15, 5:00, and 6:00 p.m.; at 7:30 it was 80 mm. systolic and 36 mm. diastolic, at 8:00 80 mm. systolic and 36 mm. diastolic, and at 9:00 80 mm. systolic and 40 mm. diastolic. His condition improved somewhat as he became conscious, but his pulse continued to be rapid and easily compressible. He continued to be cyanotic and complained of some stiffness in his joints.

Blood pressure taken at various times during the night varied between 68 and 72 mm. Hg systolic and 46 and 50 mm. Hg diastolic. He did not take fluids very well. Intramuscular injections of 10 c.c. of adrenal cortex extract were given twice.

At eight o'clock the morning after admission he was more cyanotic, his blood pressure was 70 mm. Hg systolic and 50 mm. diastolic, and his pulse was weaker than on the previous evening.

Laboratory Studies. Blood: hemoglobin 12 gm., red blood cells 5,150,000, white blood cells 34,600, polymorphonuclears 85, bands 19, juvenile neutrophiles 7, lymphocytes 7, monocytes 1. Blood sugar 95 per cent.

Serum Sodium (done through courtesy of Dr. George Berry at Strong Memorial Hospital, Rochester, N. Y.): determination No. 1 127.2 meq./L; determination No. 2 128.8 meq./L.

Throat cultures: negative for meningococci.

He was given at 9:00 a.m. intravenously: 1,000 c.c. physiological saline, 15 c.c. adrenal cortex extract, 250 c.c. whole blood.

At 10:30 a.m. he was given 5 mg. of desoxycorticosterone intramuscularly.

His condition again began to improve. He was able to give a little more history, stating that he had been perfectly well until the morning of admission when he reported to the dispensary because of headache and chilly sensations. His cyanosis lessened. The purpuric spots had by this time ceased to appear.

He was given 10 c.c. of adrenal cortex extract at 1:00 p.m. and at 8:00 p.m. and 5 mg. of desoxycorticosterone at 9:45 p.m. His pulse was of better quality, but his blood pressure during the day and night did not rise above 78 mm. Hg systolic and 58 mm. diastolic.

Adrenal cortex, 10 c.c., was given intramuscularly at 2:00 a.m. and at 6:15 a.m.

The morning of the third day he seemed considerably improved. His blood pressure was 82 mm. Hg systolic and 56 mm. diastolic, his pulse was of good quality, his neck was still slightly stiff. There was beginning fading of his purpuric rash.

The sulfadiazine was continued, the levels obtained being:

4– 8–43	16.0 mg. %	4–13–43	7.5 mg. %
4– 9–43	14.0 mg. %	4–14–43	5.0 mg. %
4–10–43	8.6 mg. %	4–15–43	6.6 mg. %
4–11–43	5.8 mg. %	4–16–43	6.7 mg. %
4–12–43	6.1 mg. %	4–17–43	7.6 mg. %

Sodium bicarbonate was administered with the sulfadiazine, 0.6 gm. with each dose. Sodium chloride was not given in tablet form as the enteric coated tablets were not available, but the patient was given saline to drink and as much salt as possible was added to the food.

Adrenal cortex extract was discontinued after the morning of the third day (April 8).

The daily dosage of desoxycorticosterone was as follows:

April 8 through April 10	10 mg.
April 11 through April 16	5 mg.
April 17 through April 18	4 mg.
April 19 through April 24	2 mg.

After this it was discontinued. During this time the patient made slow steady improvement. At no time did he have any suppression of urinary output or any edema.

His blood pressure showed a slow gradual rise, examples of it being:

April 10	100/92	April 16	120/50
April 11	100/44	April 19	120/55
April 14	110/50	April 23	124/60

(Note: his blood pressure on October 10, 1942, the date of his examination for enlistment, was 110 mm. Hg systolic and 70 mm. diastolic.)

The first six days of his course were febrile, with maximum temperatures of 104, 101.2, 102.2, 101.2, 103, and 100.9° F. on successive days; after the sixth day he had a normal temperature.

On April 11 (five days after the meningococcus antitoxin) he had a mild urticarial serum reaction.

The remainder of his convalescence was uneventful. On May 18 he was placed on a salt-free diet. He remained free of any symptoms of suprarenal insufficiency on this diet. There was no drop in blood pressure. On the tenth day of this diet the following determinations were made: serum sodium 141.5 meq./L; serum potassium 7.09 meq./L.

Further convalescence was uneventful and he was discharged to duty after a brief convalescent leave.

This case is presented in detail as an example of a patient with the full-blown picture of the Waterhouse-Friderichsen syndrome with recovery. The principal features of all the cases are shown in the various tables.

In connection with these much discussed cases the following questions naturally arise:

(1) Did this patient have adrenal hemorrhage?

(2) Was the picture of circulatory collapse due to acute adrenal insufficiency or to overwhelming bacteriemia?

(3) Did the adrenal substitution therapy play any rôle in his recovery?

These are questions that are very difficult to answer. It is almost inconceivable that a patient with the total bilateral adrenal hemorrhage found in three out of four of our autopsied cases should attain complete adrenal recovery.

Williams [3] has recently reported a series of 17 fatal cases of the Waterhouse-Friderichsen syndrome. Of these only nine showed hemorrhage into the superadrenal glands at autopsy. The clinical findings in the cases showing and not showing adrenal hemorrhages were identical. There is no way of proving that our patient had adrenal hemorrhage.

The presence of a low serum sodium suggests the possibility of adrenal insufficiency at least, but again before considering this conclusive evidence of adrenal insufficiency we should like to see some studies on the serum sodium in other fulminating bacteriemias. It is possible that we are dealing simply with the circulatory collapse known to occur in overwhelming infections. If we cannot prove the presence of adrenal insufficiency we cannot say to what extent our adrenal substitution therapy contributed to the patients' recovery.

On the other hand, we believe that in the light of our present knowledge these patients should be energetically treated.

The treatment divides itself naturally into these phases:

(1) To combat infection: sulfadiazine by the intravenous route in the same manner and dosage as in the treatment of cerebrospinal fever.

(2) To combat the hemorrhagic tendency: repeated small transfusions.

(3) To combat "toxemia": antitoxin. In the Waterhouse-Friderichsen group only are we still using the antitoxin. We have no way of knowing whether or not it helps but have given it to all of our recovered cases and to one of the fatal cases.

(4) To combat circulatory collapse and dehydration: continuous intravenous fluids.

(5) To combat possible adrenal insufficiency: a continuous infusion of 5 per cent glucose in saline, repeated intravenous injections of adrenal cortex extract and occasional intramuscular injections of desoxycorticosterone.

(6) To combat anoxemia (when cyanosis is present): an oxygen tent.

TABLE I

All Cases Summarized with Respect to Clinical Findings on Entry and Outcome

Case No.	Temp.	Pulse	B.P.	Purpura	Cyanosis	Conjunctival Hemorrhages	Coma	Peripheral Circulatory Collapse	Therapy
1	103	130	0	Marked	Yes	Yes	No	Yes	Inadequate
2		140	0	Moderate	Yes	Yes	No	Yes	No transfusion
3	106		30/0	Yes	Yes	Yes	No	Yes	No antitoxin
4	104	112	60/40	Yes	Yes	Yes	No	Yes	Inadequate
5	104	126	80/60	Yes	Yes	Yes	No	Yes	Adequate
6	105	155	84/58	Yes	Yes	Yes	No	Yes	Adequate

Outcome

Case No. 1—Died
Case No. 2—Died
Case No. 3—Died
Case No. 4—Died
Case No. 5—Recovered
Case No. 6—Recovered

In table 1 two cases are described as having had inadequate therapy. The first of these died while preparations for transfusion and adrenal substitution therapy were being completed. The second case received sulfadiazine and fluids and 10 c.c. of adrenal cortex extract. His circulatory collapse

occurred with great rapidity and the venous collapse was so striking that we were unable to give intravenous therapy. Death occurred while the attempt was being made. Of the two other cases who died, one did not have meningococcus antitoxin. The other received adequate therapy except for a transfusion. He died at the beginning of the transfusion. The recovered cases received what we consider adequate therapy, as previously described.

TABLE II

All Cases Summarized with Respect to Hematologic Findings

Case No.	W.B.C.	Percentage Polymorphonuclear Cells	Blood Platelets	Bleeding Time	Clotting Time	Prothrombin Time
1	22,000	Not done		Not done	Not done	Not done
2	Not done			Not done	Not done	Not done
3	12,550	79%	161,400	Not done	Not done	Not done
4	9,000	83%	281,280	Not done	Not done	Not done
5	18,900	92%	291,000	2 min., 40 sec.	4½ min.	Not done
6	15,500	90%	365,000	Not done	Not done	7 min.

The mechanism by which the bleeding tendency is produced is not known. The figures in table 2 demonstrate that there is no thrombocytopenia in most cases and that the bleeding and clotting times are not increased. We were not able, therefore, to confirm the theory that a substance is produced by the circulating organism which causes the platelets to be agglutinated and removed from the circulating blood.

TABLE III

All Cases Summarized with Respect to Their Bacteriologic Findings

Case No.	Nasopharyngeal Culture	Blood Culture	Demonstration of Organisms in Blood Smear	Spinal Fluid Culture
1	Negative	Negative	Plus	Negative
2	Not done	Not done	Plus	Not done
3	Negative	Negative	0	Not done
4	Not done	Negative	Plus	Negative
5	Not done	Not done	Negative	Negative
6	Negative	Positive	Negative	Not done

The occurrence of these cases in the midst of a minor epidemic of cerebrospinal fever naturally led us to believe that they were manifestations of meningococcus bacteriemia. We were disappointed in the results of our attempts to find the meningococcus in blood cultures. As shown in table 3, in only one case was a positive blood culture obtained. In one case gram-negative diplococci were demonstrated in smears from the skin lesions.

In three cases, although no growth was obtained in the blood culture, organisms morphologically resembling meningococci, both intracellular and extracellular, were demonstrated in an ordinary smear of the circulating

blood (figure 2). The cells containing meningococci superficially resemble basophiles and could easily be mistaken for them.

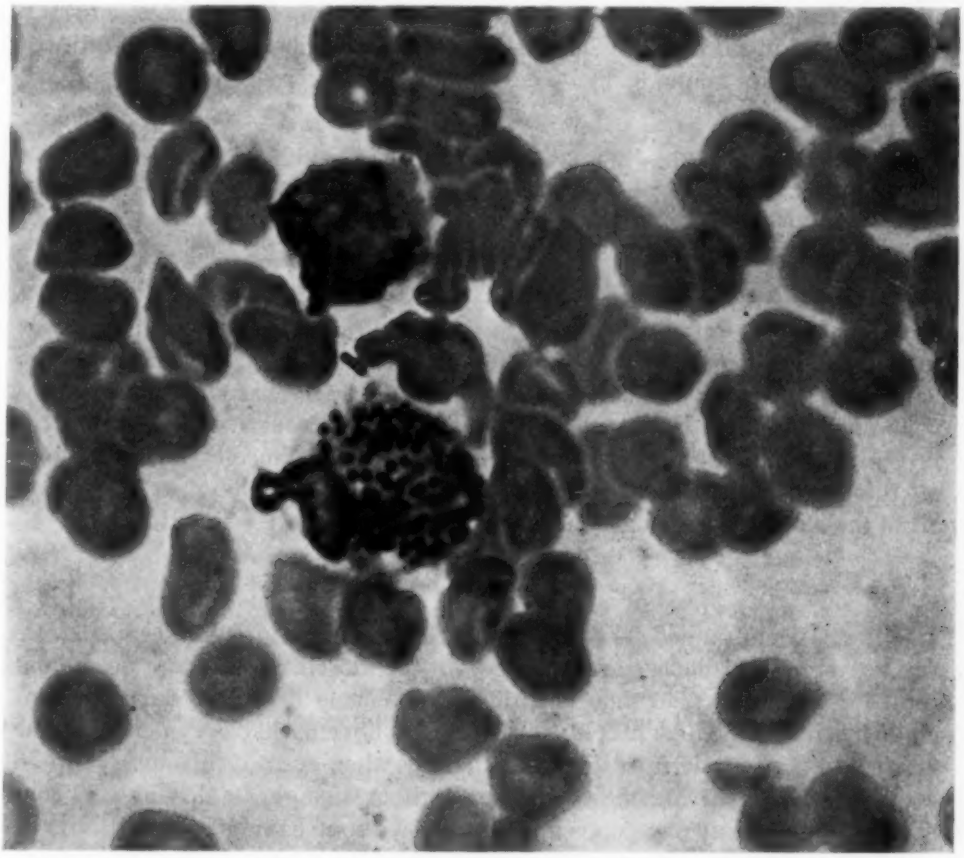

FIG. 2. Blood film from case of Waterhouse-Friderichsen syndrome showing leukocyte containing meningococci.

Table 4 demonstrates that in those cases in which lumbar puncture was done the spinal fluids were normal or showed a very slight pleocytosis. None of the cases had the physical signs of meningeal irritation.

TABLE IV

Spinal Fluid Findings in Cases Where Spinal Puncture Was Performed:

Case No.	Cell Count	Globulin	Sugar	Meningococci
1	220	Negative	58 mg.	Negative
2	Not done			
3	Not done			
4	87	Negative	65 mg.	Negative
5	2	Negative	100 mg.	Negative
6	Not done			

Necropsies were performed by Lieutenant Commander Jack Norris on all of our fatal cases. Table 5 shows the findings related to the suprarenal glands. In three out of four cases Commander Norris found bilateral adrenal hemorrhage. In the fourth case there was hemorrhage into the right adrenal gland only. The cerebral lesions described by Banks and McCartney were not found. These cases were not of the "comatose type."

TABLE V

Pathological Findings with Respect to Adrenal Hemorrhage in Fatal Cases

Case No.*	Right Adrenal Gland	Left Adrenal Gland
1	Hemorrhage	Hemorrhage
2	Hemorrhage	No hemorrhage
3	Hemorrhage	Hemorrhage
4	Hemorrhage	Hemorrhage

The alarming rapidity with which this condition, if untreated, progresses to a fatal termination makes it imperative to institute appropriate therapy with the least possible delay. Our meningitis ward was under the supervision day and night of a medical officer trained in the care of meningococcal infections. The solutions for intravenous use and the medications were kept on the ward. The laboratory expedited the cross matching so that blood from the blood bank was available in a very short time for transfusion.

SUMMARY

Our patients ranged in age from 17 to 34, the majority under 20. We realize, therefore, that we are dealing with the most favorable age group and that our results were better than they would have been had our series included infants and old people. Even so, it is remarkable evidence of the effectiveness of modern sulfonamide therapy when even in this age group 76 consecutive cases of meningitis recover without a single fatality and 50 consecutive cases of meningococcemia recover without having meningitis.

In an epidemic of meningitis it is possible that a certain number of cases will be found which have the clinical features of the Waterhouse-Friderichsen syndrome. These cases represent the group in which the greatest number of fatalities will occur, but even in them the prognosis is not hopeless and intensive therapy should be instituted. Although it is not possible to say that all cases of the Waterhouse-Friderichsen syndrome are the result of meningococcemia, the occurrence of a relatively large number of cases in the course of an epidemic of meningitis and the demonstration in three of them of the presence of meningococcus in the blood stream point to the meningococcus as an important etiological agent in this much discussed condition.

CONCLUSION

1. An epidemic of meningococcus infection at a Naval Training Station is discussed.

2. Seventy-six consecutive cases of meningococcus meningitis seen since the opening of the hospital recovered satisfactorily with sulfonamide therapy.

3. Fifty consecutive cases of meningococcus bacteriemia also recovered satisfactorily with sulfonamide therapy.

4. Six cases are discussed which presented the characteristic clinical features of the Waterhouse-Friderichsen syndrome. Two of these patients recovered.

5. Of the four fatal cases, all of which came to autopsy, three had bilateral and one unilateral adrenal hemorrhage.

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THE ANABOLIC EFFECTS OF THE ANDROGENS AND SOMATIC GROWTH IN MAN*

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In 1889 Brown-Sequard,[1] then 72 years old, injected a testicular extract into himself and felt a return of his youthful sense of well-being. Little substance remains from this early experiment in human organotherapy although historians speak of an impetus given thereby to endocrine research. Such extracts of the testis are inactive in simple objective tests, and the subjective and probably imaginative character of Brown-Sequard's response never inspired much confidence in his interpretation of testicular function. Nevertheless the very prominence of this experiment in the history of endocrinology has served to keep alive Brown-Sequard's guiding thought that the testis might exert some invigorating influence upon human somatic tissue. The physician aware of the manifestations of precocious puberty has often reflected on the meaning of the frequent association between advancement of somatic growth and sexual maturation. It has occurred to him that the androgens themselves might share in the construction of non-genital tissue although until recently he has lacked the experimental means to press the point home. Some of these suggestive pathological circumstances may be briefly recalled.

The interstitial cells of Leydig are commonly considered the site of male hormone production by the testis. Tumors of these cells are rare indeed, and only in a few instances is there any considerable evidence for increased production of an androgenic secretion. Five such cases have been described in children. Sacchi [2] in 1895 described a nine and one-half year old boy who beginning at five showed exceptional growth in height, weight and musculature, associated with development of a penis 9 cm. long, a deep voice, a beard and masculine body hair. He eventually reached a height of 4 feet 9 inches and came to weigh 97 pounds. This is some 6 inches taller and some 30 pounds heavier than the average American nine year old. A large tumor of the left testis weighing 289 grams was removed and was found to be comprised of epithelioid cells bearing inclusions thought by Sacchi to be coccidia. This interpretation of the inclusions is usually discounted and the essential lesion held to be an interstitial cell tumor, although all doubts as to

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the nature of the process cannot now be resolved. Subsequently beard hair and much body hair disappeared, but the moustache remained, the voice became softer, and erections subsided. Ten months later there was no further change, and general habitus was specifically mentioned as remaining unaffected by the operation.

In 1929 Rowlands and Nicholson [3] described a nine year old boy who appeared 18. He was 5 feet tall, powerfully built, with a deep voice, hair on the chest, loins and pubis and a fully developed penis. Unusual growth had been first noted at six years of age, voice changes at seven. A large tumor of the left testis was removed and several pathologists agreed it was comprised of interstitial cells. Two years later there was no regression of the signs of puberty and the boy still shaved regularly. He had grown only ¾ of an inch further in height. Abdominal exploration incidental to an appendectomy at this time showed no evidences of metastases.

In 1932 Sutherland [4] reported a muscular boy of 11 with a large penis, abundant pubic hair, and sufficient facial hair to necessitate shaving. Unlike the first two patients he was said to have been short although the actual height was not given. The epiphyses of all the long bones had united. A large right testis was comprised entirely of masses of lipoid rich Leydig cells. The subsequent history of this boy is unknown.

In 1936 Stewart, Bell and Roehlke [5] described a five year old boy of good physical and mental development. Although not regarded by the authors as exceptionally tall, his height of 51 inches exceeds the average for American boys of his age by some five inches. During the preceding year his penis had enlarged until it was 10 cm. long. Sparse pubic hair was present and his voice was slightly low. The left testis was of normal size. The right testis was considerably larger, bearing a firm tumor 1 cm. in diameter. This tumor was composed of interstitial cells. Curiously the adjacent testis tubules showed all stages of spermatogenesis short of spermatozoa production. Seventeen months after removal of the enlarged testis the boy was well with no evidence of further progression of signs of puberty.

In 1942 Werner and his colleagues [6] described a boy six years and nine months old who was 4 feet 6 inches tall and 74 pounds in weight. This was considered some 6 inches taller and some 20 pounds heavier than normal. His muscles were overdeveloped for his age and roentgenograms disclosed "markedly advanced bone development." Considerable hair growth was apparent over the pubis and scrotum and some increased growth was discerned on the upper lip; his phallus was large, measuring 3¾ inches long; his prostate was palpable, his voice deep in tone and his facial expression mature. Frequent erections and an affectionate interest in girls on at least one occasion had been noted. This process was of at least a year's duration. The right testis bearing a circumscribed subcapsular tumor, 1.2 cm. in diameter, was removed. The cells comprising the tumor were held to be interstitial cells in all likelihood, in part by virtue of their similarity to the

interstitial cells proliferating in mice under the influence of stilbestrol. The possibility of an adrenal cortical rest tumor was likewise entertained. Following removal of the tumor the coarse hair on the boy's upper lip disappeared and his demeanor was regarded as gentler. However, his growth in height continued, amounting to 1.75 inches in eight months, with a corresponding increment of 5 pounds in weight.*

In these five patients the signs of precocious puberty could with some reason be ascribed to overproduction of testicular androgens by interstitial cell tumors. It is true that no autopsy was performed in any instance and that some doubt as to the nature of the epithelium proliferating in the testes clearly exists in two of these cases. The need for careful examination of the neoplastic cells is shown by the remarkable boy described by Wilkins, Fleischmann and Howard [7] in which bilateral adrenal hyperplasia was accompanied by massive growth of adrenal-like tissue in the testes. Accepting, however, the probable accuracy of the several authors' interpretation of the lesions and taking into account the clinical improvement usually resulting from excision of the testicular growths, we may consider that we possess a fair picture of the effects of excessive testicular secretion in the growing boy. With the possible exception of the case of Stewart, Bell and Roehlke, all of the affected subjects showed manifest skeletal and muscular alterations. Three of these four boys were large at the time of examination and had given a history of rapid growth. The fourth was short by virtue presumably of exceptionally early ossification of his epiphyseal cartilages. All four of the boys were muscular.

A somewhat similar association between skeletal and muscular growth and advancement of the more familiar signs of puberty is well known when the adrenal cortex is the source of the androgens and when lesions of the hypothalamus and pineal and juxta-pineal areas induce precocious puberty.

In the course of normal development an association between the earlier phases of sexual maturation and enhanced somatic growth is well known. Thus the data of Gray and Ayres [8] for boys show an increase in percentage gain in height and weight early in puberty, followed by a drastic decline as growth ceases. Inspection of the data provided by Richey [9] suggests that on the average the earlier such a sign of puberty as axillary hair appears, the earlier the pubertal growth increment occurs. The same relationship between the time of growth spurt and age of menarche is apparent in the data of Richey and of Shuttleworth [10] on girls. There is a scarcity of detailed information on muscular growth, but Baldwin's [11] measurements of muscle

* In 1941 Huffman [64] reported a 6 year old boy who had had gradual enlargement of the left testicle for two years. A sparse amount of pubic hair was present and both breasts were slightly enlarged. Measuring 51 inches in height and weighing 60 lb., he was regarded as somewhat advanced physically although no actual history of accelerated growth was obtained. A tumor comprised of trabeculated cords of lipoid bearing epithelium was removed. Two years later both pubic hair and the breast enlargement persisted although no evidence of recurrence or metastases could be found. This case was inadvertently omitted from the above series.

strength by the hand dynamometer indicate that the masculine superiority in muscle strength becomes well defined in the later years of adolescence.

In recent years the mechanism of this association between somatic and sexual development in man has become clearer, although many points remain to be explained. An account of this matter begins properly with the experiments of Kochakian and Murlin [12, 13, 14] in the castrate dog. Between 1935 and 1937, these workers demonstrated that urinary androgens, androstenedione and testosterone induced a prompt and sustained decline in urinary nitrogen excretion, accounted for by reduced urea excretion, and unaccompanied by any elevation of the concentration of nitrogenous constituents in the blood. Fecal nitrogen excretion was not affected. They pointed out that there was a maximal effect in the neighborhood of 0.05 gm. of nitrogen stored per kg. per day which could not be exceeded by increasing or protracting the dosage of the androgen. On cessation of treatment a rebound hypernormal excretion of nitrogen could often be detected, although all retained nitrogen was not regularly promptly lost. As a site of protein deposit the genital accessories came naturally to mind. In 1936, however, Korenchevsky, Dennison and Brovsin [15] noted as had others the somewhat reduced weight of the castrate male rat and found that the liver, heart and kidneys were smaller than normal. Testosterone restored these organs to normal size and increased body weight. These authors spoke accordingly of an anabolic property of the androgens in a more general sense.

In 1937 Thorn and Harrop [16] called attention to the fact that the chemical relationships between the sex hormones and several steroids of the adrenal series were reflected in a common capacity to induce sodium, chloride and water retention. Whatever the mechanism of these effects might be it was clear that non-genital tissues were involved in the response.

When sexually underdeveloped men and boys began to receive testosterone propionate by intramuscular injection it became apparent to several observers that notable gains in body weight usually occurred within the first few weeks of treatment. In our own experience this increase in weight amounted to 3.0 to 9.0 kg. at the maximum and might be accompanied by slight and non-progressive edema of the face and ankles and by an increase in appetite.[17] This process was self-limited, plateaux appearing in 40 to 70 days despite continued treatment. This same gain in weight has now been shown to occur after methyl-testosterone given orally and this same plateau is well seen in a chart given by McCullagh and Rossmiller.[18]

When such subjects as the eunuchoid J. X (figure 1) were placed in the hospital on a constant diet and their activity regulated this same gain in weight was observed.[19, 20] Urinary nitrogen excretion was conspicuously affected. From a level of 7.4 grams per day (figure 1) there was a steady decline to 4 grams per day beyond which further treatment made little difference. Other experiments demonstrated that urea was the affected fraction,[19] that fecal nitrogen was not influenced [21] and that the concentration of

the nitrogenous constituents of the blood—plasma proteins, hemoglobin, non-protein nitrogen and urea—was not increased.[19, 20] Since nitrogen is retained in the body chiefly as protein, one may estimate here the amounts of protein stored. In 25 days J. X. retained 346 grams of protein. Since the combined weights of the normal seminal vesicles and prostate do not exceed 50 grams and changes in these structures are not prominent to palpation within this time, it is clear that growth of the accessory genitalia accounted for very little of the retained material.

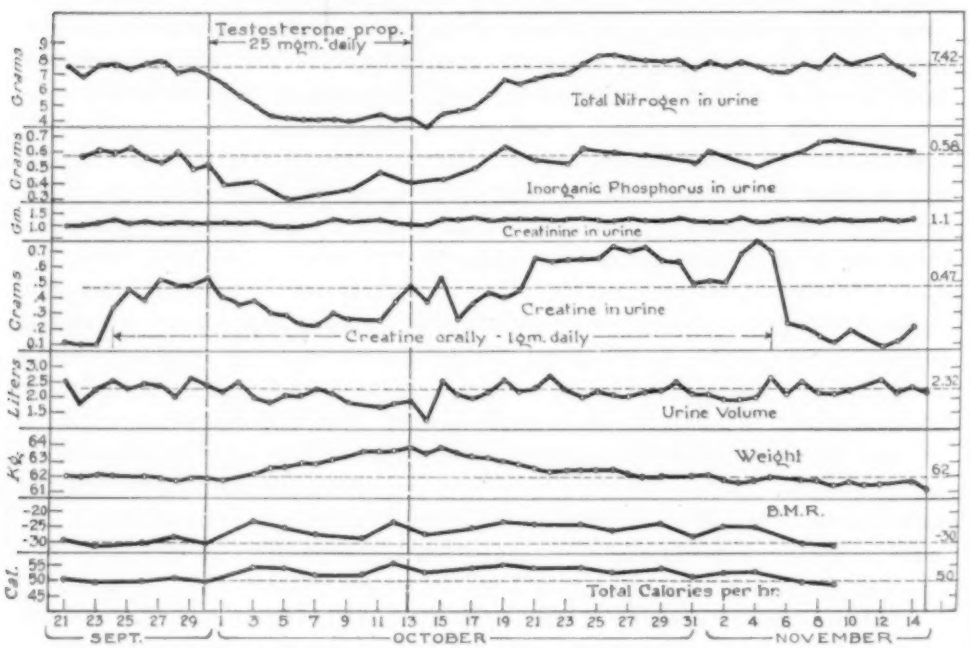

FIG. 1. The effect of testosterone propionate given intramuscularly on several urinary constituents, body weight and basal metabolic rate of the eunuchoid, J. X. The figures to the right designate pre-treatment baselines. From Kenyon, et al.[20]

On cessation of treatment nitrogen excretion returned to normal but in 38 days of continuous observation no conspicuous compensatory loss of the retained material could be demonstrated (figure 1, figure 2, experiments in sequence). We have seen this phenomenon in another eunuchoid (M. D.) observed for 21 days after cessation of therapy.[19] This is not invariable and it is possible that loss of retained nitrogen may be much more evident when treatment has been protracted to the point of saturation of affected tissues. Thus in J. K. (figure 4), treated for two months, a compensatory loss of nitrogen was in progress at the end of the experiment. The disposition of the eunuchoid organism to bind retained protein as tenaciously as it often does is a matter of great interest. It indicates that the androgen may promote the incorporation of the protein into some structural form which does not require

androgens thenceforth for its maintenance. As a parallel the larynx which does not involute notably on withdrawal of testosterone may be cited. In the rat, Sandberg, Perla and Holly [22] described diminished retention of nitro-

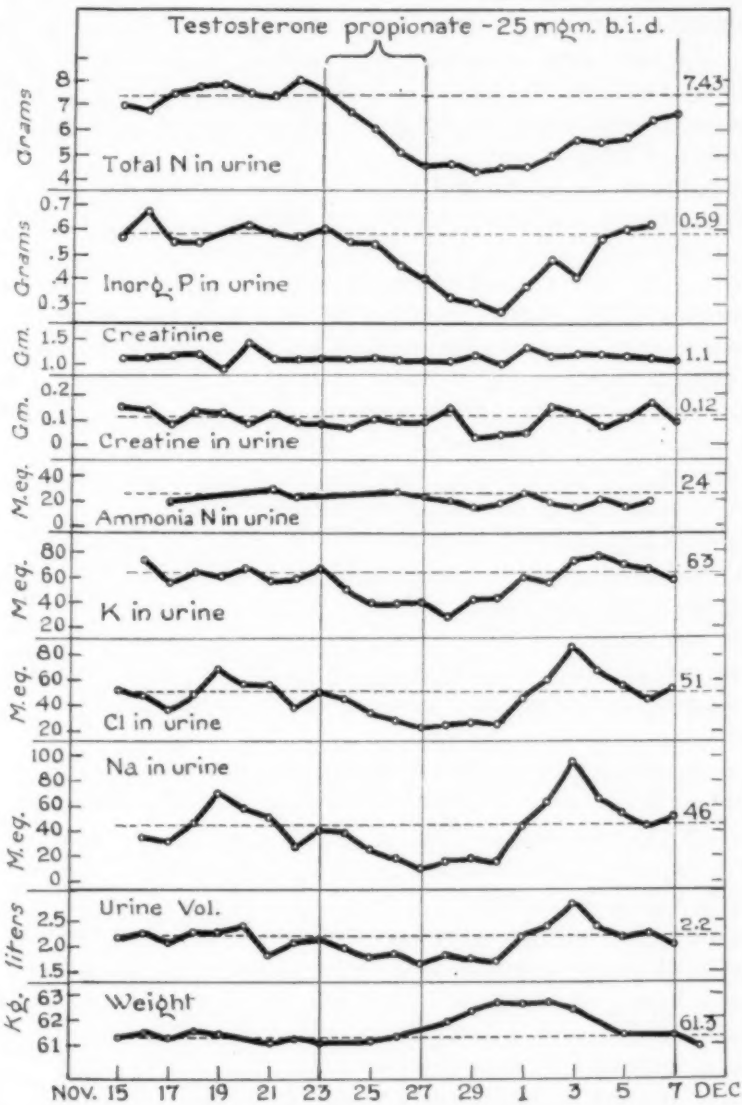

FIG. 2. The effect of testosterone propionate given intramuscularly on several urinary constituents and body weight of the eunuchoid J. X. The figures to the right designate pre-treatment baselines. From Kenyon, et al.[20]

gen and associated tissue constituents after castration during the period of rapid growth. Neither there, however, nor in adults did loss of nitrogen supervene. Such studies after castration in man are greatly needed but

will be difficult to execute. The absence of obvious loss of somatic tissue in boys with interstitial cell tumors after removal of the offending neoplasm [2, 3, 6] may have its explanation in this persistence of structural changes after withdrawal of the inciting androgen.

Associates of nitrogen in tissue are similarly affected by testosterone propionate. We have now repeatedly seen urinary sulfate decline in parallel with urinary nitrogen (figure 5).[21, 23, 24] The ratio of nitrogen to sulfur estimated as retained often but not always approximates the normal ratio of these elements in body protein.

As first shown by Thorn and Engel [25] in the normal dog and in an impotent man urinary inorganic phosphorus declines in parallel with urinary nitrogen (figures 1, 2, 5, 7).[20, 21] Fecal phosphorus is unaffected in brief experiments [21] and the concentration of inorganic phosphorus in the serum is not increased.[20, 21] After cessation of treatment the curve of urinary phosphorus excretion usually maintains a reasonably close conformity with that of urinary nitrogen but in some instances a dissociation is seen,[23, 26] phosphorus being discharged while nitrogen is still being retained. We have thus far demonstrated no alteration of calcium metabolism in the eunuchoid in experiments of brief duration,[21] so that most of the phosphorus retained here may be conceived as accompanying nitrogen rather than calcium. Calcium retention has, however, been observed by Albright, Parson and Bloomberg [27] as a delayed phenomenon in subjects with Cushing's syndrome receiving testosterone propionate and may, we believe, be eventually demonstrated in the eunuchoid with suitably protracted experiments. The substantial skeletal growth of undergrown boys achieved with several androgens, and to be subsequently described, certainly attests to calcium retention in such individuals.

If the creatine content of the eunuchoid's urine is considerable or if creatine excretion be sustained at high levels by ingestion of creatine, creatinuria is reduced by testosterone propionate (figure 1).[19, 20, 21] Similar observations have been described in the rat,[28] rabbit,[29] and monkey.[30] Since creatine is so largely segregated in striated muscle and is so important there, and since loss of creatine through the urine is so common in disorders wasting muscle, one is tempted to see a specific and useful influence on muscle metabolism represented here. However this may be, the recent studies of Wilkins, Fleischmann and Howard demonstrate that creatinuria may be increased rather than decreased by methyl-testosterone given either orally [31] or intramuscularly [32] to the undergrown, sexually under-developed boy. Samuels and his associates [33] have likewise induced creatinuria in the normal man with methyl-testosterone. Both groups conceive of increased creatine production under the influence of this androgen. This discrepancy between the effects of testosterone propionate and methyl-testosterone is somewhat surprising and needs explanation. In both the eunuchoid [34] and the dwarfish sexually retarded boy [31] methyl-testosterone induces much the same nitrogen retention

as does testosterone propionate. If one may judge from an experiment with chorionic gonadotropin [24] the effects of the testis hormone itself more nearly correspond to those of testosterone propionate than to those of methyl-testosterone in its influence on creatine metabolism. That much obscurity still surrounds the influence of the androgens on creatine excretion is further exemplified by Duckworth's inability to modify the creatine tolerance of young boys with testosterone propionate.[59]

In brief experiments urinary creatinine is not affected by testosterone propionate. In longer experiments, however, urinary creatinine may rise in time (figure 4). This may signify an increase in muscle mass. Similar increases in urinary creatinine were well seen by Wilkins, Fleischmann and Howard [31] in their underdeveloped, undergrown subjects receiving methyl-testosterone orally.

Accompanying the decline in urinary nitrogen, inorganic phosphorus and sulfate during treatment with testosterone propionate a more irregular reduction in excretion of sodium, chloride and potassium occurs together not infrequently with a decline in urinary volume (figure 2).[19, 20, 25] This decline in sodium, chloride and water excretion is analogous to that induced by the chemically related adrenal cortical steroids, by desoxycorticosterone in both dogs and men with and without adrenal insufficiency,[35, 36, 37] and by corticosterone in dogs at least.[35] These effects may be exerted through the same renal mechanism. Reduction in urinary potassium excretion, however, is unlike the effects of any known adrenal steroid, adrenal extracts and desoxycorticosterone inducing potassium diuresis. It is likely that potassium retained during treatment with testosterone is associated with protein in the new tissue formed. On cessation of treatment the retained sodium, chloride and water are sharply discharged as body weight is lost. Retained potassium is usually less completely lost, following more nearly the pattern of nitrogen.

Some analysis of the composition of the weight gain under the influence of testosterone propionate is now possible.[19, 58] If three grams of water be assumed deposited with each gram of protein, the weight so accounted for is considerably less than the actual weight increment in a short experiment (figure 3). Furthermore, during recovery from the androgen effect weight is lost at a time when nitrogen is still being retained. Water associated with retained sodium and chloride in extracellular fluid compartments of the body during treatment accounts for much of the weight gain and diuresis of such salt and water for most of the weight loss at this time. The indications are, however, that in longer experiments protein and associated water may constitute a more substantial portion of the weight increment (figure 4). Certainly expansion of extracellular fluid never proceeds to the point of troublesome and progressive edema in the eunuchoid.

Basal heat production in the eunuchoid characteristically rises slowly during treatment with testosterone propionate [19, 38] and in J. K. (figure 4)

reached a point 38 per cent above the initial level when expressed in total calories per hour, or 24 points in the B M R. Similar findings are recorded by Thompson and Heckel.[39] When more nearly replacement levels of testosterone propionate are injected (25 mg. 3 × weekly) the elevation in basal metabolic rate is quite irregular and averages only about 10 per cent.[38] Large doses of methyl-testosterone orally up to 300 mg. daily, may actually elevate the basal metabolic rate to as high as + 40, as shown by McCullagh

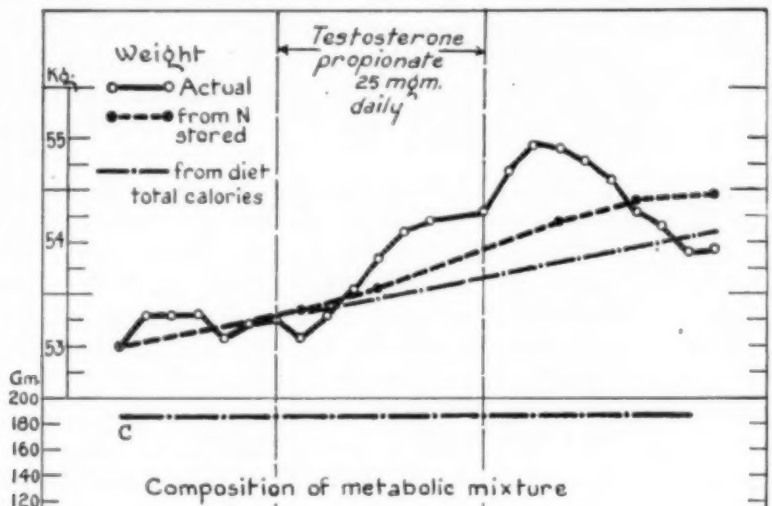

FIG. 3. The composition of the weight gain and of the metabolic mixture of the eunuchoid N. D. under the influence of testosterone propionate. In estimating the weight gain from N stored it was assumed that 3 grams of water were stored with each gram of protein. The interrupted line serving as the baseline in the upper compartment was the predicted weight gain derived after subtracting total caloric expenditure (insensible weight loss) from caloric intake. We are indebted to Dr. A. H. Bryan for this chart. From Kenyon et al.[19]

and Rossmiller.[40] In dwarfs smaller amounts of methyl-testosterone were calorigenic.[32] The mechanism of the increase in heat production is obscure, but it seems likely that both increased active protoplasmic mass and increased heat production per unit mass are involved.[38]

Distinct metabolic effects may be induced in the eunuchoid or the pubescent boy with as little as 5 mg. of testosterone propionate per day (figure 4).[21, 24, 38] This is of considerable importance in the assignment of physiological significance to these reactions as such a dose falls below most estimates of adult replacement requirements. Such estimates range from

50 to 150 mg. weekly based on maintenance of secondary sex characters and urinary androgen levels. Thus, it is possible that small amounts of testicular secretion may exert significant anabolic influences at times when the more familiar evidences of hormonal action are not prominent. It should be recalled at this point that accelerated somatic growth is an early manifestation of puberty in the boy.

It is quite possible to sustain nitrogen retention in the eunuchoid for as long as two months (figure 4),[38] at which time as much as 1.8 kg. of

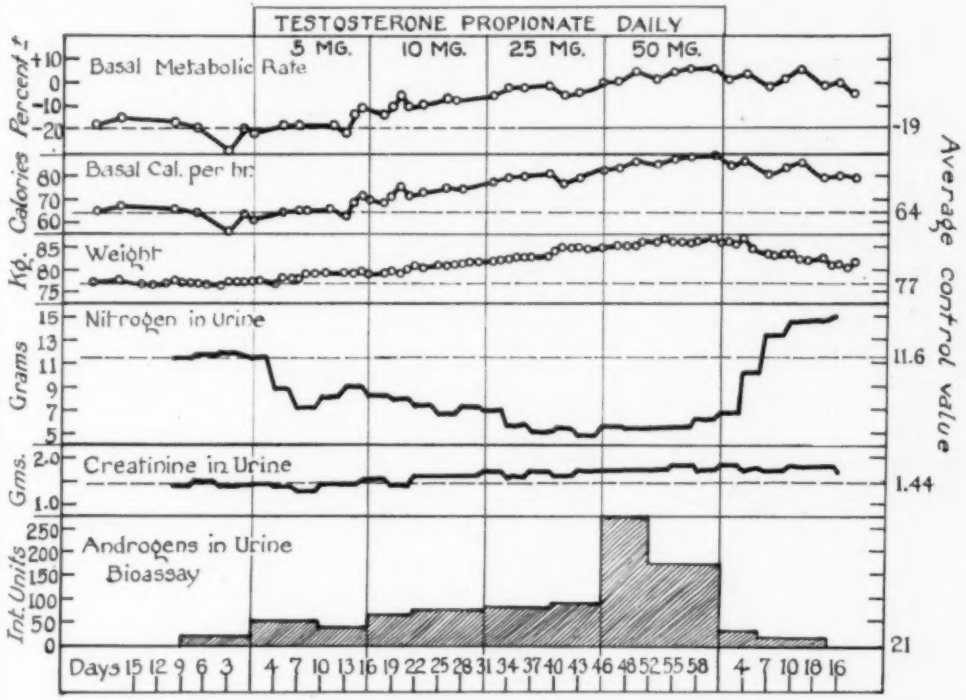

FIG. 4. The effect of testosterone propionate given intramuscularly in progressive increments to the eunuchoid J. K. on urinary nitrogen, androgens, body weight and basal heat production. From Sandiford et al.[38]

protein may be estimated as deposited. Albright, Parson and Bloomberg [27] demonstrated an even more extended influence on nitrogen, calcium and phosphorus retention in Cushing's syndrome. If one may judge from the plateaux of the weight curves, however, there must come a time in eunuchoids when the body can no longer so respond. This time limit has neither been defined nor studied and the compensating forces are obscure. In the child it is likely from the growth curves given that the anabolic effects of the androgens can be sustained for months to years.

Although testosterone propionate is not as yet known to possess any properties unlike those of the internal secretion of the testis, it is most desirable to compare any somewhat unfamiliar response to the synthetic androgen

with the corresponding response to the testis secretion. In a short boy of 12 just entering puberty spontaneously, chorionic gonadotropin was seen to exert as much or more influence on the urinary excretion of nitrogen, inorganic phosphorus, inorganic sulfate and creatine as 5 mg. of testosterone propionate (figure 5).[24] The effects on sodium and potassium excretion, although less striking, seem much the same for the two substances and the respective incre-

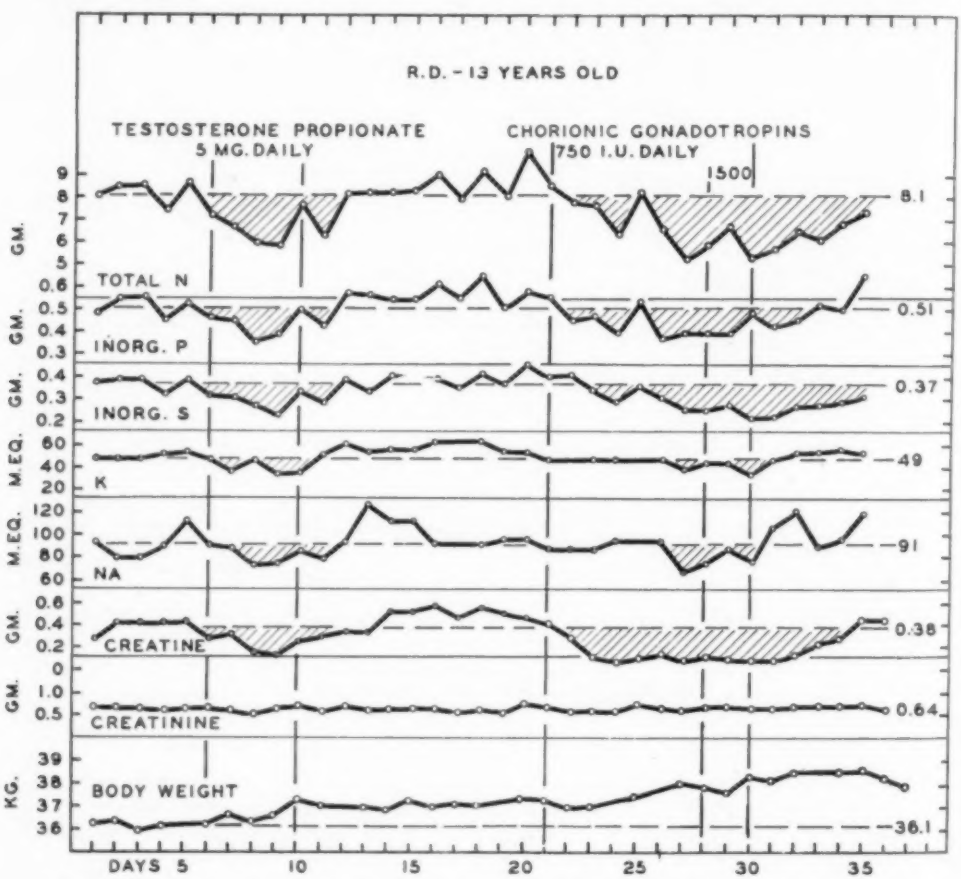

FIG. 5. The comparative effect of testosterone propionate and chorionic gonadotropin on several urinary constituents and body weight of the pubescent boy R. D. From Kenyon et al.[24]

ments in body weight correspond. Since it is likely that the effects of chorionic material were mediated through the testes there are no grounds adduced here for distinguishing between the metabolic effects of the testis secretion and testosterone propionate.

The retention of nitrogen, sulfur, phosphorus and potassium suggests the growth of cellular mass under the influence of testosterone propionate and chorionic gonadotropins and at once recalls the enhanced somatic growth of

boys with interstitial cell tumors of the testis described by Sacchi, Rowlands and Nicholson, and Werner and his associates. As a matter of fact several physicians [41, 42, 43] treating boys with chorionic gonadotropins had noted growth spurts during the time of augmented testicular activity. Dorff [41] who was among these has recently provided a detailed comparison of the short identical twins, Joseph and Richard. Their curves of growth in height,

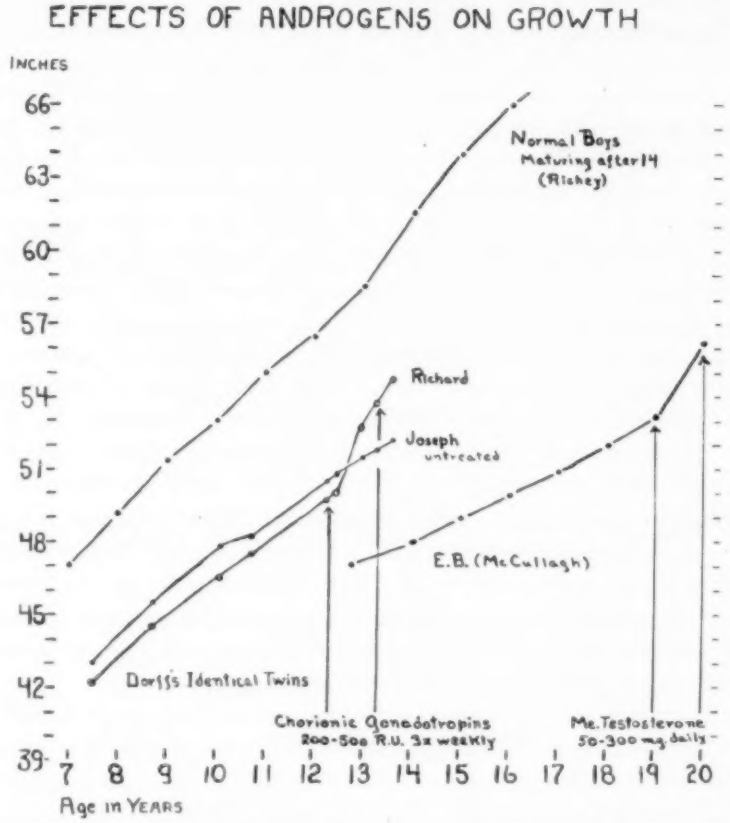

FIG. 6. The effect of chorionic gonadotropins on growth in height from Dorff [41] and of methyl-testosterone from McCullagh and Rossmiller.[18] As a control curve the data from Richey [9] for slowly maturing normal boys in whom axillary hair appeared after the age of 14 are utilized.

given in figure 6, proceeded in parallel fashion until Richard received a pregnancy urine gonadotropin. He then rapidly outstripped Joseph. The weight curves not shown here run a similar course. During treatment Richard's phallus grew, pubic hair appeared and his voice deepened while Joseph remained sexually childish. Webster and Hoskins [44] described eight boys with retarded genital development who received testosterone propionate. They grew an average of 1.36 cm. per 100 days before treatment, 3.6 cm. per 100 days during treatment and 1.56 cm. per 100 days after treatment was stopped. The rate of growth was thus more than doubled during the

androgen effect. Browne and Ross [45] and Thompson and associates [43] have noted similar results. McCullagh and Rossmiller's dwarf E. B. charted in figure 6 [18] grew 3 inches in 10 months at the age of 19 during treatment with methyl-testosterone orally. Data provided by Wilkins, Fleischmann and Howard [31, 32] are in agreement in describing growth promoting properties of methyl-testosterone in short boys with poor sexual development.

Several observers agree that the ossification centers of the long bones and of the hands expand during treatment of the underdeveloped boy with chorionic gonadotropin.[41, 42, 43] Thompson, Heckel and Morris,[43] for example, record an increase of three and one-half to four years in bone age during 12 months of such treatment. There is slight evidence as yet for induction of premature ossification of the epiphyseal cartilages by either chorionic material or synthetic androgens. It has been difficult conclusively to further ossification of the long persisting cartilaginous discs of the adult eunuchoid with testosterone propionate. Considerable time is certainly required for such an influence to become apparent and the disposition of these cartilages to disappear slowly and irregularly in the untreated eunuchoid makes uncertain the significance of such obliteration as may occur during protracted treatment. Premature epiphyseal closure in the long bones in association with other evidences of androgen activity does occur, however, in precocious puberty. This strongly suggests that androgens in sufficient amount for a long enough time will advance ossification of these cartilages and hence terminate growth in height. Such termination of growth does not appear to supervene as a rule until some stimulus to elongation of the extremities has been exerted, although Sutherland's case [4] seems to be an exception. It is quite clear that if androgens readily and promptly promoted ossification of the epiphyseal cartilages, normal puberty in the boy could not be synchronized as it is with a phase of accelerated growth in height.

Less is known of the influence of androgens upon trunk length or limb length as such, little of the extant data having been analyzed in such specific segmental terms. Augmentation of sitting height is a prominent phase of normal pubertal growth and the trunk appears to be especially sensitive to the growth promoting effects of androgens according to the experience of Thompson, Heckel and Morris.[43] Exacting anthropometric study of such material is much to be desired and will yield valuable information.

It is likely, therefore, that the testis hormone has at least two influences upon the growth of the skeleton. The first, apparent during the early years of androgen production, results in bone growth without ossification of the epiphyseal cartilages; the second influence, apparent later when androgen production is higher and has been sustained longer, results in ossification of the epiphyseal cartilages of the long bones and is associated with the cessation of linear growth of these bones. This second influence needs much better experimental illustration than is now available.

The retention of several constituents of tissue under the influence of

androgens in short experiments is thus seen to be the chemical expression of growth exemplified by the increments in stature and body weight of treated children. It should be noted that calcium retention expected during such a phase of rapid bone growth has not yet been demonstrated in subjects other than women with Cushing's syndrome [27] and aged men with osteoporosis,[55]

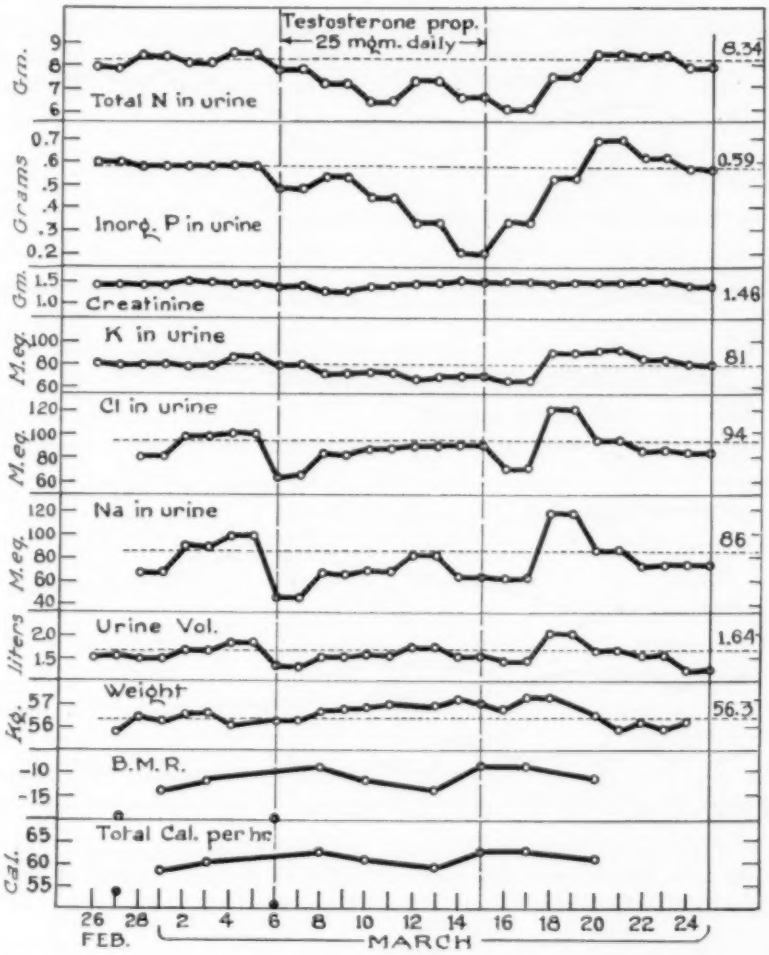

FIG. 7. The effect of testosterone propionate given intramuscularly on several urinary constituents, body weight and basal metabolic rate of the normal young man R. W. From Kenyon et al.[20]

presumably because experiments of suitable duration have not as yet been undertaken. Sites of new tissue deposit under the influence of androgens require further elucidation. The prominence of muscular hypertrophy in boys with precocious puberty and the apparent muscular growth observed in certain boys and eunuchoid men under treatment combine in stressing the likelihood that skeletal muscle acquires new substance under these circum-

stances. Papanicolaou and Falk [46] have demonstrated hypertrophy of the temporal muscles of the castrate male or female guinea-pig receiving testosterone propionate. The functional consequences of this presumed skeletal muscle growth in man require much more specific description than is now available, although two reports [47, 48] of increased strength and diminished fatigability in eunuchoids receiving testosterone propionate have been re-

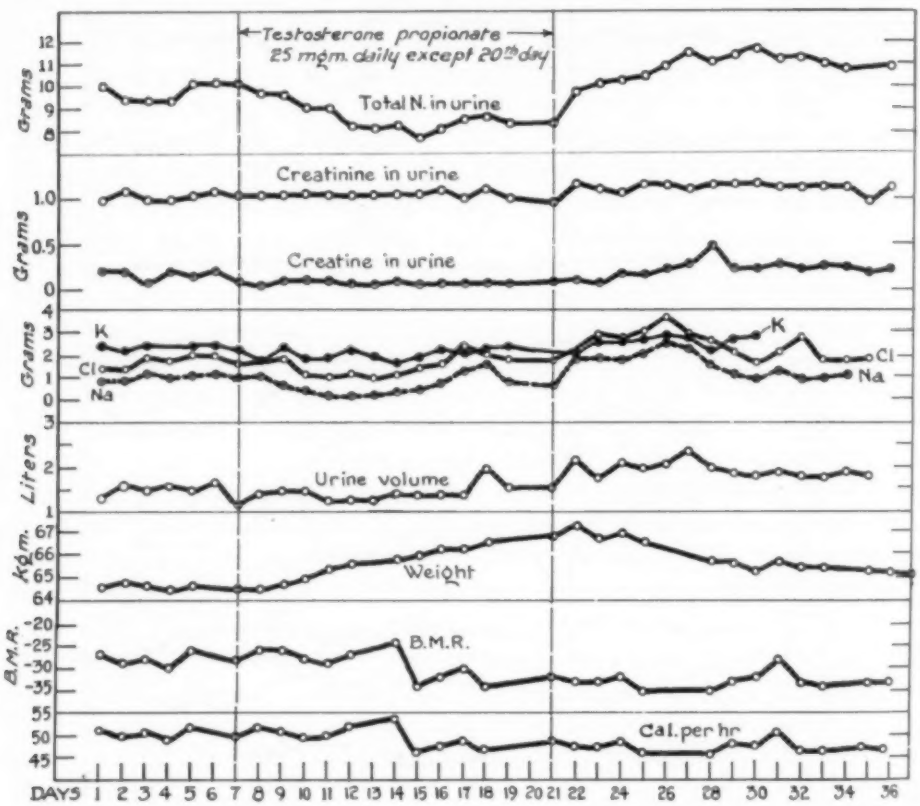

FIG. 8. The effect of testosterone propionate given intramuscularly on several urinary constituents, body weight and basal heat production of the eunuchoid H. S. with hypopituitarism. From Kenyon, et al.[19]

corded. Such effects would be expected from consideration of the abnormal strength often mentioned in boys with precocious puberty and from the masculine superiority in muscle power most distinct during and after adolescence. In normal men, however, Samuels and his associates [33] were unable to increase muscle strength by methyl-testosterone.

Other organs than muscle may serve as sites of new tissue deposit in man. McCullagh and Jones [60] have recorded an eventual increase in the number of circulating red cells in the eunuchoid receiving androgens. We have spoken of the emphasis given by Korenchevsky and his associates [15] to the restoration of the weights of kidneys, livers and hearts of castrate male rats to normal

levels by testosterone propionate. This response of the kidney of the rat has been further described [49] and striking renal tubular hypertrophy in the mouse has been induced by testosterone and testosterone propionate by Selye [50] and Pfeiffer, Emmell and Gardner.[51] Kochakian and Clark [52] have initiated an instructive analysis of enzymatic mechanisms involved in such tissue growth. Welsh and his associates [53] have described an increase in "functional tubular mass" (diodrast T M) in female dogs receiving testosterone propionate without alteration in the rate of glomerular filtration or in effective renal blood flow, and Lattimer [61] noted some increase in glomerular filtration as well and recorded an increase in renal mass at autopsy in this species. In relatively brief experiments Lattimer could not decisively increase either glomerular filtration or functional tubular mass in endocrinologically sound men with one or two kidneys unless compensatory hypertrophy following unilateral nephrectomy was well underway. He did, however, find that the kidneys of the normal male weigh 12 per cent more per kg. body weight than those of the female during adult life but not during infancy. This is compatible with the view that the androgens may increase renal mass in man in time.

It is now appropriate to consider some of the conditions influencing the metabolic effects of testosterone propionate insofar as these are understood. In the castrate dog, according to Kochakian and Murlin, and in the eunuchoid, according to our own work, there exists a maximum intensity of nitrogen retention per day in response to administered androgens, which cannot be exceeded by increasing the dosage or by protracting treatment. The testes of the normal young man, however, are not necessarily exerting this maximum possible influence. Thus, in figure 7 both urinary nitrogen and inorganic phosphorus declined characteristically during the injection of testosterone propionate into a normal 20 year old, and both constituents were firmly retained for at least a brief period thereafter. There is in all likelihood less nitrogen retention than in the eunuchoid. Our two normal young men receiving 25 mg. of testosterone propionate per day have retained 30 mg. of nitrogen per kg. per day at the time of maximum response as compared to 63 mg. per kg. per day as an average of six experiments on five eunuchoids (range 53 to 80). This quantitative distinction between the reactions of normal and hypogonad individuals is less clear with respect to other affected constituents of tissue. Thorn and Engel [25] similarly have described metabolic effects of testosterone propionate in an impotent but endocrinologically sound man and in a normal dog. Tolerance to ingested creatine seems to constitute an exception. Sutton [54] could not improve the already considerable capacity of normal men to dispose of creatine by treatment with testosterone propionate.*

* Venning, Hoffman and Browne [62] point out that Masson's description [63] of the remarkable absence of cachexia in adult men suffering from malignant interstitial cell tumors of the testes with widespread metastases may be due to excessive amounts of the anabolic testis secretion. Such a man was shown to excrete enormous amounts of androsterone sulfate in the urine.[62]

Even in advanced age reduction in urinary nitrogen, inorganic phosphorus, sulfate, sodium and potassium and increases in body weight have been readily induced by our group,[28] and retention of nitrogen, phosphorus and calcium by Reifenstein and his colleagues.[55] The intensity of response was as great in our experience as in normal young men. Among our own eunuchoids no real difference in intensity of effect was noted over an age range of 20 to 51.

Since the aging process itself does not seem to limit seriously the metabolic response to androgens the question arises as to why a positive balance of affected tissue constituents is not apparent throughout adult life. It must be assumed that some as yet obscure opposing process intervenes with force sufficient to counteract such metabolic influence as the normal testis is able to exert. It is of more than passing interest that the properties of the adrenal steroid 17-hydroxy-11-dehydrocorticosterone as described by Thorn and his coworkers [56] seem on the whole well adapted to such a purpose. However this may be, the forces limiting growth with the onset of full maturity are as fascinating as those promoting growth. In his analysis of the effects of testosterone propionate on the growth rate of the castrate rat Rubinstein [57] has pointed out that, although one level of dosage will promote somatic growth, a higher level will inhibit such growth. The hypothesis that large amounts of the androgen will inhibit the secretion of the growth promoting hormone by the pituitary gland is offered and is worthy of serious consideration in the study of the growth plateaux of maturity.

The sexually underdeveloped [21] or normal young woman [20] may respond very well to the metabolic influence of testosterone propionate, demonstrating that neither the asexual feminine constitution nor normal feminine hormones interpose insuperable obstacles to the androgens. Growth in height and weight of dwarfish girls given small amounts of methyl-testosterone orally has been described by Wilkins, Fleischmann and Howard.[31, 32] Pubic hair proliferated, but slight deepening of the voice and growth of the clitoris necessitated discontinuing treatment in one girl but not in the other.[32] Further attention to dosage might well obviate the disadvantageous effects. Certainly the metabolic response is a sensitive one and it is possible that those obscure androgens of the normal woman may serve some useful metabolic purpose and play some rôle in the normal girl's growth.

Since the anterior lobe of the pituitary body is known to secrete a hormone stimulating growth it might be reasonable to suppose that the androgens act through this gland in exerting anabolic effects. It is difficult to conduct an impeccable clinical experiment on this point since some residual pituitary tissue may survive nearly any destructive process in man. A 24 year old eunuchoid of ours had an enormous suprasellar cyst and very little if any pituitary tissue left at autopsy.[19] His urinary nitrogen declined distinctly with testosterone propionate (figure 7) as did his urinary sodium and chloride and he gained 2 kg. in weight. His nitrogen retention of 25 mg.

per kg. per day was less than in other eunuchoids, however, and the retained material was more completely dissipated than usual on cessation of treatment. Albright and his colleagues [58] have fully confirmed this observation in dwarfs with numerous physiological evidences of hypopituitarism and obtained growth in height and weight in these subjects.* Little likelihood exists, therefore, that testosterone acts solely through the hypophysis in inducing nitrogen, salt and water retention. Data of our own [26] and of Talbot, Butler and MacLachlan [65] indicate likewise that the adrenal cortex is not an essential intermediary since fully normal reductions in urinary nitrogen, inorganic phosphorus, sulfate, sodium, potassium and creatine have been induced in subjects with Addison's disease. The elevation of the basal metabolic rate and enhanced creatinuria induced by methyl-testosterone have been produced in a cretin.[32] Thus, as far as is now known the metabolic effects of the androgens examined in sufficient detail are exerted directly upon tissues without the intervention of other organs of internal secretion. This is in accord with concepts of zoölogists concerning stimulation of growth of genital accessories and development of secondary sex characters in lower forms.

Although all of the evidence summarized here points to the conclusion that the testis under the impetus imparted by the anterior lobe of the pituitary contributes to the somatic growth of the child and probably does so for several years, it cannot be held that it is ever the sole determiner for such growth. Hypogonadism does not mean dwarfism. The pre-pubertal castrate or the eunuchoid is if anything tall and his long bones seem to have grown exceptionally well. It may be that the growth of the trunk is retarded by virtue of testicular insufficiency but this is difficult to prove. It is likely in so far as the skeleton is concerned that the testicular hormone simply accelerates certain processes of bone development which would proceed more slowly to the same end without it. This, we take it, is the view of Thompson, Heckel and Morris [43] who have given the problem considerable thought. The ossification of epiphyseal cartilages of the long bones may be taken to illustrate this concept. In the presence of the testes ossification proceeds normally, in their absence it is delayed but eventually occurs none the less. In other somatic structures the testis is essential for certain final phases of growth. This is clearly true for the larynx and for the hair follicles of certain regions and it may well be true for the skeletal musculature.

It is unwise to presume at present that the somatic influences of the testis hormone taken alone are such as to provide for a harmoniously developed individual at any time in life. The anterior lobe of the pituitary body and the thyroid gland surely make their own independent contributions. The temptation to accelerate the growth of the smallish slowly developing boy who has not as yet received the full pubertal impetus from his own glands of

* Werner and West [66] have noted nitrogen retention and creatinuria after methyl-testosterone in adults with Simmonds' disease.

internal secretion should be resisted. Nothing in our knowledge of uncomplicated hypogonadism encourages us to believe that shortness is ever a permanent consequence of testicular insufficiency when this is the sole defect. When pituitary insufficiency can be demonstrated or when growth and genital retardation persist sufficiently long to be clearly pathological there is no reasonable objection to the use of the androgens or pregnancy urine preparations. Observations on such people made with care will tell us in time how far we can go in achieving acceptable body structure with only one hormone.

The association of somatic growth and great muscular development with other manifestations of androgen activity in subjects with adrenal cortical tumors or adrenal hyperplasia strongly suggests the presence in the organism of some agent much like testosterone in its manifold effects. The nature of this agent is unknown, but its possible rôle in the normal economy invites speculation and research.

It is not to be supposed that all somatotropic effects of steroid hormones described here are irretrievably bound up with androgenicity in the more familiar sense. Thus estradiol benzoate in large doses produces many effects like those of testosterone propionate.[21] Among these are retention of nitrogen, inorganic phosphorus and sodium. These influences may be demonstrated in both hypogonad men and women, but their physiological significance for growth of the girl requires much further elucidation.

Summary

1. The extant data on precocious puberty in boys with interstitial cell tumors of the testis is reviewed and the association of somatic growth with the more familiar aspects of androgen action is described.

2. Testosterone propionate and chorionic gonadotropin are shown to induce retention of nitrogen, inorganic phosphorus, sulfate and potassium in amounts so large as to necessitate the assumption of increase in the mass of non-genital tissue. Methyl-testosterone has similar properties at least in several respects. Sodium and chloride are also retained for a period with these agents. Calcium retention can be induced in certain subjects with testosterone propionate. Creatinuria may be reduced by testosterone propionate but is increased by methyl testosterone. Basal heat production in the eunuchoid may be increased by testosterone propionate and methyl testosterone.

3. Growth in height and weight of the undergrown underdeveloped boy may be produced by chorionic gonadotropin, testosterone propionate or methyl testosterone. Maturation of bony structure occurs but closure of the epiphyses is not readily induced and presumably requires prolonged and heavy dosage.

4. The testis is accordingly conceived as exerting profound general anabolic effects and thus accelerating the somatic growth of the boy. It is possible that feminine androgens similarly influence the growth of the girl.

5. Certain non-genital sites of new tissue deposit in man under the influence of the androgens seem strongly suggested. These are the skeleton and the skeletal musculature. The kidney and other organs may well be affected.

6. The anabolic effects of the testis do not appear to be exerted either through the anterior lobe of the pituitary body or through the adrenal cortex.

7. The mature normal testis is not exerting this anabolic or somatotropic influence to the fullest extent to which the organism can respond.

8. Since age does not seriously limit the metabolic response to the androgens, unknown opposing forces must operate to achieve the nitrogen equilibrium characteristic of maturity.

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MALARIA IN THE ARMY *

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ANY effort to evaluate the potential importance of malaria in the army must be based upon consideration of its immediate effects during the war and its more remote effects after demobilization. Its immediate importance lies in possible high morbidity and non-effective rates. Later, returning military and naval personnel may introduce the disease into areas of this country in which malaria has been absent for many years, and augment its incidence and severity in other areas where it is normally endemic. Both of these possibilities imply a relatively high infection rate in military personnel.

Comparison of the geographical distribution of the present theaters of operations with the world distribution of malaria (figure 1) indicates that much of the present war must be fought in areas where the disease is highly endemic. Complete protection of the great numbers of men involved would constitute an almost impossible task, even in peace time. In time of war, and especially under conditions of jungle warfare or those of rapidly moving mechanized campaigns, the available measures for malaria control are limited and relatively less effective. Control or elimination of anopheline breeding is obviously difficult. There remains protection of the individual against the individual mosquito by the use of nets and repellents, the use of so-called prophylactic treatment, and the spray killing of adult mosquitoes.

Complete protection against the bite cannot be accomplished, especially under combat conditions. Prophylactic or suppressive treatment has enjoyed an unmerited reputation based upon a widely accepted misconception. Strictly speaking there is no such thing as drug prophylaxis, since none of the antimalarials will prevent infection. When properly used, however, they are effective in controlling the intensity of infection and preventing the clinical phenomena of acute malaria during the period of adequate administration. Following withdrawal, however, acute malaria frequently occurs and its subsequent course, with respect both to severity and the incidence of relapses, is largely unmodified by the previous suppressive therapy.

These factors, therefore, provide strong support for the two basic contentions that large numbers of individuals will be exposed to infection, and that until new developments augment existing measures of protection, such exposure will inevitably lead to a high rate of infection. Furthermore, such infection will produce a situation quite different from any that exists in the United States, even in areas of the south where the disease is endemic. This depends upon certain features characteristic of the disease

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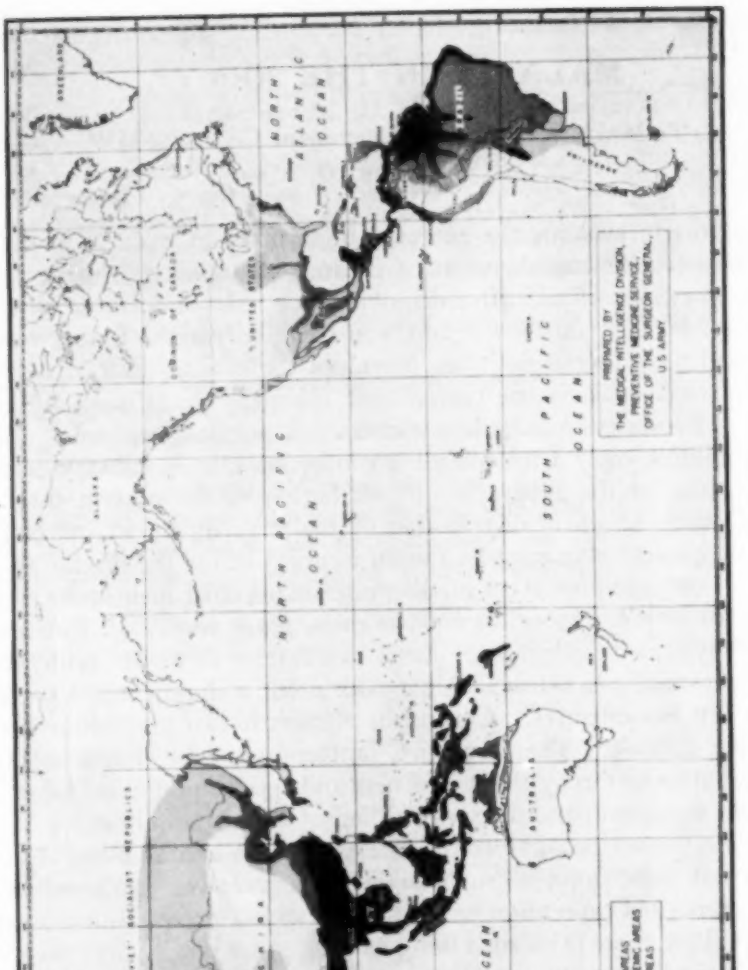

FIG. 1. Malaria.

in areas of high endemicity which are absent in regions of low endemicity, and consequently are seldom understood or appreciated by those who have not studied malaria in hyperendemic areas in the tropics. It likewise depends upon certain fundamental biologic relationships between the plasmodium and the infected human host.

The malaria of the tropics is predominantly the malignant tertian or aestivo-autumnal form produced by the *Plasmodium falciparum,* which, unlike simple tertian and quartan malaria, frequently presents grave and fatal complications. This characteristic difference in severity appears to be due in large part to certain biologic characteristics of the *P. falciparum.* Unlike *Plasmodium vivax* which predominantly parasitizes reticulocytes,[1] *P. falciparum* invades both reticulocytes and mature erythrocytes [2] producing a more rapidly developing and a much more intense parasitemia. Furthermore, the physical state of the parasitized cells is altered. They tend to adhere to capillary endothelium and to each other forming both thrombi and emboli. The resulting disturbances of local circulation undoubtedly determine the extremely diverse clinical phenomena which are so typical of malignant tertian malaria. These two features, the rapidly developing parasitemia, and the vascular interference are among the important reasons for early and accurate diagnosis of the type of malarial infection.

A further misconception is widely held concerning the action and effectiveness of the antimalarial drugs. Although they will check the acute clinical phenomena and reduce an intense parasitemia to submicroscopic levels, they will not in all instances completely eliminate the plasmodia. In consequence the disease often characteristically relapses throughout a variable period of time. Termination of the clinical phenomena appears to depend in part at least upon the development of a satisfactory immunity which seems to be both cellular and humoral in nature, and not alone upon the action of a drug.[3, 4] In experimental human malaria this immunity has been shown to be relatively firm but strictly strain specific. No protection is conferred against infection by heterologous strains, and the homologous immunity is not permanent.

It is unquestionably this factor of acquired immunity, together with the universal susceptibility of the uninfected human being, which determines the characteristics of malaria in a people indigenous to a hyperendemic zone. In such a region there is a high transmission rate and continuous reinoculation. There is a high infant mortality rate, and a high incidence of acute clinical malaria among surviving children. Those who reach adult life apparently have sufficient immunity or tolerance of their infection to be relatively free from clinically active disease despite the persistence of the plasmodia in their blood. There is, therefore, the apparent paradox of a high incidence of acute disease in children and a relatively healthy adult population. In areas of low endemicity on the other hand, *Plasmodium vivax* predominates and the incidence of acute malaria is distributed through all age groups but is not highly

prevalent in any. The uninitiated entering either region and limiting his observations to the adult population can be easily and dangerously misled.

The problem which our men are facing in many tropical areas is that of the children born in such area, not that of the partially immune adult population who have survived invariable and severe childhood malaria and who have acquired tolerance to their persisting parasitemia. Our men will constitute a large body of non-immunes which in the presence of a heavily parasitized indigenous population, and an efficient anopheline vector, provide all the requirements for the occurrence of malaria in epidemic form.

Such a background naturally stimulates inquiry concerning past experience of armies operating in malarial regions. The nature of military training operations and field maneuvers even in peace time entails a greater exposure of military personnel than a protected civilian population encounters in the same general area. Thus, in Panama the malaria rate for the army since 1912 has been consistently and considerably higher than that for the civilian employees. Military subposts situated in unsanitated areas, most of them inadequately screened, have had extremely high rates. In 1936, 18 per cent of the malaria occurred in these posts among 2.5 per cent of the Department strength.[5]

In the first World War malaria played an important rôle, and in certain instances determined the outcome of campaigns. In Macedonia three armies facing each other, the British, French, and German, were immobilized by the plasmodia. The French in 1916 could put only 30,000 men in the field out of a total force of 120,000. The British forces had 30,000 cases in 1916, and 70,000 in 1917. The average allied strength in Africa during those two years was about 50,000 and from this there were 120,000 cases of acute malaria.

The possibility that personnel returning from tropical service may introduce malaria widely into the United States must not be underestimated. The freedom of the northern states from this disease for years past makes this seem unlikely in the eyes of many. However, *Anopheles quadrimaculatus,* the important malaria vector in the south, extends well into the northern tier of states and will prove to be an efficient transmitter if a sufficient human reservoir of infection is available. Precedent for this possibility is provided by both England and Germany after the last war, when returning infected troops were the source of localized outbreaks of malaria among the civilian population.

The loss of the Dutch East Indies and the cutting off of the quinine supply has created a degree of fear that is totally unwarranted by the facts. Contrary to general belief, quinine is not an essential drug for suppressive or so-called prophylactic treatment, nor for the treatment of acute clinical malaria. The Fourth General Report of the Malaria Commission of the League of Nations, in fact, states that atabrine is slightly more effective in

the control of acute malaria than is quinine, and that 0.3 gram atabrine is equivalent therapeutically to 1.0 gram of the latter drug.[6] It has likewise been found at least equally effective for suppressive treatment, and for certain individuals it is preferable to quinine.

The therapy of malaria has two objectives—the prompt control of acute and often dangerous clinical phenomena, and reduction of the incidence of the late relapses which may reach 50 per cent in benign tertian or vivax infections. Here again atabrine when followed by a three day course of plasmochin in dosage of 0.01 gram T.I.D. gives better results than quinine. The experience of Callender and Gentzkow in Panama suggests, however, that the mode of administration must vary for *P. falciparum* and *P. vivax* infections if the maximal reduction of the relapse rate is to be obtained. In the former, the best results were observed when atabrine 0.6 gram was given the first day and 0.3 gram daily for the ensuing seven days, followed by a three day course of plasmochin. In vivax infections, on the other hand, the optimal results were obtained by a single dose of atabrine 0.6 gram daily for four days, likewise followed by a three day course of plasmochin.[7] This requires additional study and if confirmed will constitute a further and important indication for emphasis of the necessity not only for a diagnosis of malaria, but for accurate identification of the type of malaria. It is necessary, however, to emphasize that it has not yet been possible to obtain the fundamental scientific data essential for exact standardization of therapy. The requirements in terms of weight of drug per unit of body weight, and relationships between blood levels and therapeutic efficacy still remain to be ascertained. Until such standards are available there must continue to be much conflicting opinion and dogma concerning a variety of suggested therapeutic regimes.

Despite these past experiences of armies and civilian groups, the possible immediate and remote importance of malaria in this war must be regarded both with caution and with reassurance; caution, because the plasmodium unquestionably presents a hazard of no small magnitude; reassurance, because the risk is generally recognized and because we are well equipped to combat it. The army and navy in tropical service are well supplied with bed-nets, head-nets, gloves, insect repellents, insecticides, and drugs for the control of the disease. The army, the navy, and the United States Public Health Service are well aware of the potential hazard of the returning gametocyte carrier and are developing plans to deal with this problem. With proper cooperation by local health authorities and practicing physicians there is, therefore, no reason to anticipate the development of a serious malaria situation. There is, however, need for instruction of practitioners concerning the extremely varied clinical picture which the disease may produce, the confusing syndromes which result from its combination with familiar endemic diseases, and the importance of early and accurate diagnosis.

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CORONARY HEART DISEASE: ANGINA PECTORIS, ACUTE CORONARY INSUFFICIENCY AND CORONARY OCCLUSION *

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HEART disease, especially coronary heart disease, is the chief cause of death and morbidity in this country. Its importance has not been emphasized sufficiently. Military personnel, more than others, lack the appreciation of the prevalence of this disease.

According to the U. S. Census report,[1] there were 385,191 deaths from heart disease in 1940, giving a mortality rate of 292.5 per hundred thousand, the largest number of deaths ever recorded for heart disease.

Since 1900, there has been a tremendous increase in heart disease after the age of 35. The changes that have taken place between 1900 and 1940 are remarkable and are shown in table 1 which is taken from figures in the U. S. Census report of 1940. This increase in heart disease is due to an increase in coronary heart disease and has resulted from a longer life span.

TABLE I

Deaths from Heart Disease

	1940	1900
Under 1 year	17.5	147.8
1–4 years	3.6	15.0
5–14 years	8.0	23.3
15–24 years	14.0—	28.8
25–34 years	29.7	43.4
35–44 years	91.7	80.8
45–54 years	279.5	173.0
55–64 years	713.5	414.1
65–74 years	1,723.5	957.3
75 and over	4,813.2	1,819.7

An editorial in the *Journal of the American Medical Association* in 1943 [2] emphasizes how frequently coronary artery disease, specifically coronary artery occlusion, causes deaths of physicians. But to those who still persist in the belief that physicians and other "sedentary" persons are peculiarly prone to coronary heart disease, let me remind them that the physician in industry believes that only the laborer or workman develops coronary heart disease. The fact is that no occupation has any priority on this disease.[3, 4]

A few years ago my colleagues and I, in collaboration with the New York State Department of Health,[5] demonstrated that more than a half million attacks of coronary occlusion occurred yearly in this country. The work

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The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

was done statistically by sampling death certificates. As time has passed it seems probable that the figure is more than a million, so that about 3,000 attacks take place daily in this country. In people over 40 years of age, a coronary occlusion develops in at least one male in every 50 and in one female in every 180 each year.

Actual postmortem examination bears out this high incidence of coronary heart disease and, specifically again, coronary artery occlusion. Thus the postmortem room of a large general hospital,[6] which represents a good cross-

TABLE II

Incidence of Various Types of Heart Disease in Cardiac Deaths in Autopsied Cases, 1917 to 1918*

Year	Total No. of Cases	Coronary Artery Disease			Rheumatic Heart Disease	Luetic Heart Disease	Congenital Heart Disease	Subacute Bacterial Endocarditis	Miscellaneous
		Acute Occlusion	Chronic	Total					
		%	%	%	%	%	%	%	%
1917	16	13	7	20	56	0	0	24	0
1918	19	5	10	15	53	5	10	16	0
1919	21	5	10	15	55	5	5	20	0
1920	17	0	18	18	48	3	0	13	18
1921	25	12	16	28	40	4	4	24	0
1922	23	21	9	30	43	4	4	0	19
1923	58	3	28	31	36	5	5	12	10
1924	33	9	21	30	36	12	0	15	6
1925	55	11	20	31	37	5	5	17	5
1926	60	7	37	44	31	8	4	8	5
1927	68	9	18	27	47	9	6	7	4
1928	61	11	19	30	42	8	6	8	6
1929	53	11	11	22	41	7	6	17	6
1930	65	15	20	35	32	5	3	14	10
1931	65	18	24	42	42	2	3	5	5
1932	77	20	28	48	20	7	5	12	9
1933	66	24	18	42	29	3	5	9	12
1934	51	26	12	38	26	4	4	8	20
1935	54	43	17	60	31	0	0	9	0
1936	70	30	10	40	34	3	6	13	4
1937	108	30	16	46	32	2	4	8	8
1938	70	46	16	62	24	2	2	7	2

* From Jr. Mt. Sinai Hosp., 1942, ix, 658.

section of the New York City population including children and adults, has shown that since 1935 coronary artery disease, especially coronary occlusion, has been the chief cardiac cause of death (table 2). In 1938, coronary artery occlusion was found in 46 per cent of cardiac deaths, outnumbering rheumatic heart disease almost two to one. Before 1925, on the other hand, one-half the deaths were attributed to rheumatic heart disease, less than one-third to coronary artery disease and coronary occlusion was thought to be rare. Thus a relative and absolute increase in the incidence of coronary artery disease, chiefly occlusion, has occurred and this is explained in two ways. First, the increasing life span has meant more victims in the older age groups for arteriosclerotic heart disease. The second explanation is the increased accuracy in diagnosis, especially in coronary artery occlusion.

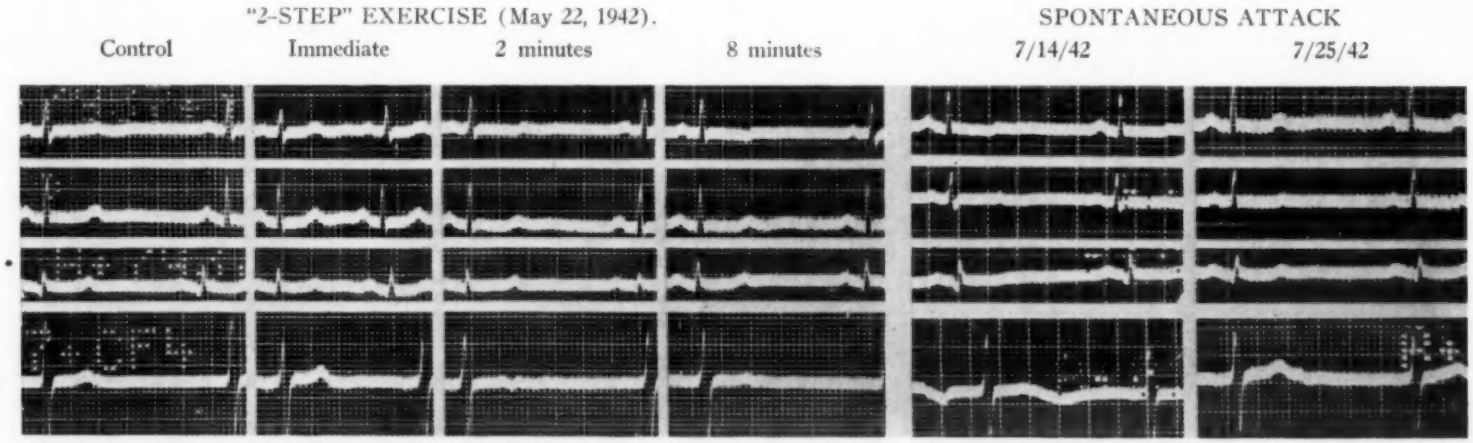

FIG. 1. G. R. P., m, 65. May 22, 1942. Examination for vague precordial "aches". Control electrocardiogram normal but following the "2-step" test T_{1-4} became inverted.

On July 14, 1942 an attack of coronary heart disease with severe chest pain for which the patient was hospitalized. T_{1-4} inverted and T_2 isoelectric. Return to normal tracing July 25, 1942.

TABLE III

	Angina Pectoris	Coronary Insufficiency	Coronary Occlusion
Mechanism	Short period of anoxemia of heart muscle	Prolonged ischemia of the heart muscle with necrosis, but without occlusion of the coronary artery.	Complete closure of the coronary artery with infarction of the heart muscle.
Physiology	Vasospasm? Disproportion between work of the heart and the coronary blood flow.	Disproportion between work of the heart and the coronary blood flow.	Complete obstruction of coronary flow.
Pathology	None.	1. Artery—Variable involvement. From normal to severe sclerosis. 2. Muscle—Focal disseminated involvement, often microscopic. 3. Subendocardial, base of papillary muscles. 4. No mural thrombosis with embolization. 5. No pericarditis.	1. Artery—Invariably diseased. 2. Muscle—Confluent, massive infarction. 3. Through and through from endocardium to pericardium. 4. Mural thrombosis with embolization. 5. Pericarditis.
Predisposing	Coronary sclerosis.	Coronary sclerosis. Hypertension, occasionally (or not uncommon). Enlarged heart. Aortic stenosis. Aortic insufficiency. Syphilitic coronary arteritis.	Coronary sclerosis. Hypertension, common.
Exciting cause	1. Exertion, excitement, food, cold, adrenalin, insulin, intravenous glucose, etc.	1. Same as for simple attack angina pectoris. 2. Gastro-enteritis. 3. Excessive tobacco plus liquor. 4. Tachycardia. 5. Hemorrhage. 6. Operation. 7. Shock, or fall in blood pressure. 8. Heart failure. 9. Infection. 10. Trauma.	None. 6. Operation? 7. Shock, or fall in blood pressure?
Age	Usually 40–70.	Usually 20–70.	Usually 50–70.
Pain	Vague, anywhere on anterior chest.	Variable, usually severe and fairly prolonged, precordial or substernal.	Severe, prolonged, substernal usually.
Effect of nitroglycerine	Relieves.	Variable, may relieve.	Not relieved; may aggravate.
Nausea and vomiting	None.	Uncommon.	Common.
Heart and circulation:			
Shock	None.	Rare except as a cause.	Common.
Heart sounds	No change.	1. No change usually. 2. Gallop rare. 3. No pericardial rub.	1. Poor, embryocardia. 2. Gallop. 3. Rub.
Blood pressure	No change or rise.	No change usually.	Definite fall.
Tachycardia and arrhythmias	None.	Uncommon.	Common.
Failure	None.	Uncommon.	Common.
Lungs		Clear.	Often congested.
Vital capacity		Usually unchanged.	Definitely diminished.
Blood velocity		Usually unchanged.	Diminished frequently.
Venous pressure		Usually unchanged.	May be increased.
Fluoroscopy	Normal.	Normal.	Systolic expansion or reversal.
Fever	None.	None or slight.	101°–103° usually.
Leukocytosis	None.	None or slight.	Constant.
Sedimentation rate	Normal.	Normal or slight.	Rapid.
Glycosuria	None.		Often present.
Azotemia	None.		Often present.
Electrocardiogram	Normal or 1. RS-T depressions. 2. T-wave inversions. 3. No Q-waves.	Characteristic pattern: 1. RS-T depressions. 2. T-wave inversions. 3. No Q-waves.	Specific pattern: 1. RS-T elevations progressing to deeply- 2. Inverted T-waves. 3. Large Q-waves. 4. Reciprocal relation. Leads I and III.
Duration of changes	Few minutes or hours.	Days and weeks.	Months.
Condition after attack	Good.	Usually good.	Poor.
Duration of illness	Few seconds to a few minutes.	Few days to weeks.	Weeks to months.
Degree of recovery	Complete.	Usually complete.	Prolonged illness, earmarks of attack for years.
Prognosis of attack	Leads to attacks of coronary insufficiency or coronary occlusion.	Fatal outcome rare.	Fatal outcome not uncommon.

Not only is heart disease of general importance, but it plays a significant part in the war emergency. We know it is a prime cause of rejection of recruits for the armed forces. The effort syndrome (neurocirculatory asthenia) is ever present with us.[7] Rheumatic fever occurs sporadically and at times reaches epidemic proportions.[8] Coronary heart disease, too, is common in men over 30 and 40 [9] but is continually overlooked. It must be that military men think that if they risk life and limb in planes, ships, and on the battlefield, arteriosclerosis cannot catch up with them.

Men with coronary heart disease are not fit for general service; they break down. This is so true that I believe every man and particularly every officer over 30 or 40 should be examined for latent coronary disease and routinely put through some standardized effort test such as the electrocardiogram after the "2-step" [10, 11, 12] exercise every year and on leaving with a task force. At the National Naval Medical Center we see coronary heart disease frequently. Even with the control electrocardiogram normal latent coronary insufficiency may be present and should be searched for (figure 1). The electrocardiographic changes appearing after the "2-step" exercise are exactly reduplicated in the same patient when low oxygen (10 per cent) is breathed, thus confirming that the changes are due to anoxemia of the heart muscle (figure 2).

We have all been reading that this or that high ranking German general has been recalled because of a heart attack, but, the wish clouding our better judgment, we rejected the official explanation and preferred to believe that it represented a quarrel between Hitler and his staff. It doesn't seem to occur to us that German officers, like American officers, will suffer attacks of coronary disease unless some swifter agent than arteriosclerosis will strike them first.

A correct terminology in the discussion of coronary heart disease is important (table 3).[13, 14] There is confusion as to the connotations of "angina pectoris," "coronary insufficiency" and "coronary occlusion." Thus, some authors use the term "coronary insufficiency" to include all forms of coronary heart disease. Although "coronary occlusion" is considered by nearly all to indicate a complete 100 per cent closure of a coronary artery, we find two recent articles [15, 16] with the words "coronary occlusion" or "coronary thrombosis" in the title and yet in the postmortem protocols there is the definite statement that the coronary vessels were patent, albeit sclerotic. The authors were apparently using the terms coronary occlusion synonymously with coronary sclerosis.

Let us now proceed to define the terms angina pectoris, coronary insufficiency and coronary occlusion.[13, 14, 17] By angina pectoris due to coronary disease is meant a transitory episode of anterior chest pain brought on by exertion, excitement, food, cold, tobacco, etc. It is due to a temporary ischemia and is not accompanied by any acute pathological changes in the myocardium. The duration of the pain is usually a few seconds to a few

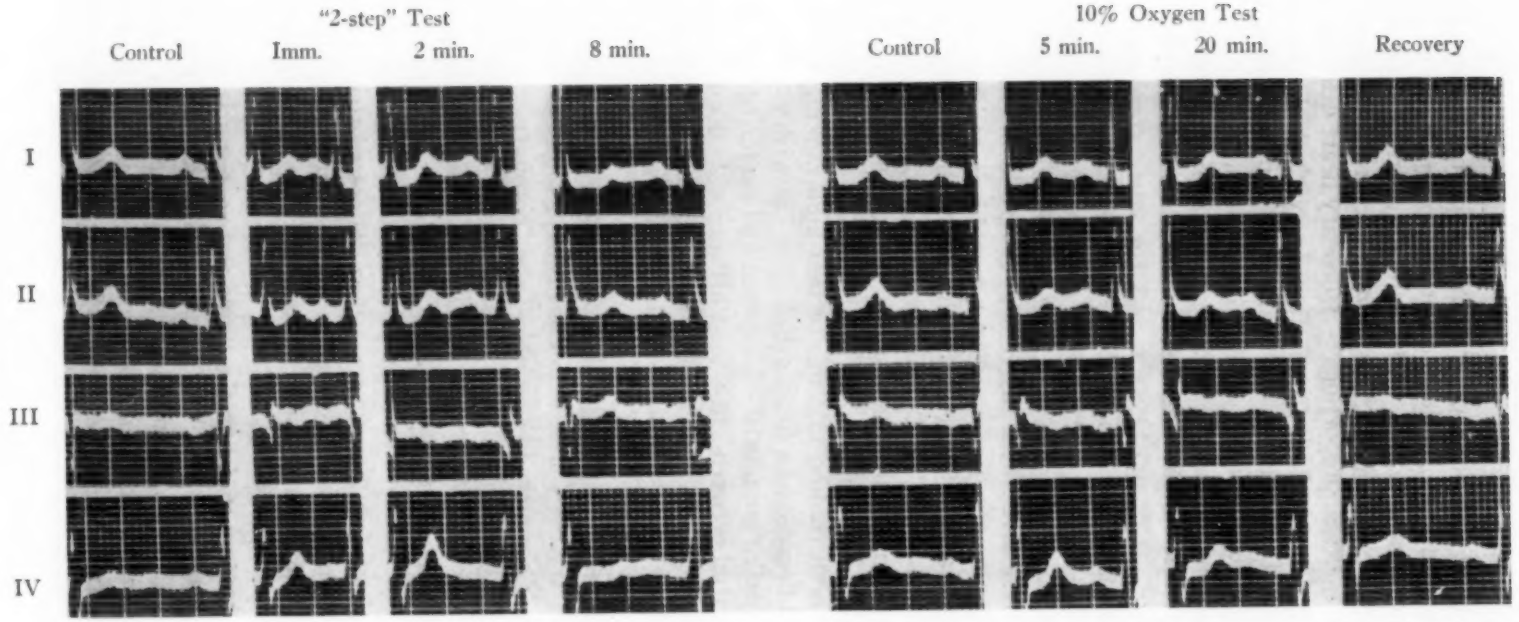

FIG. 2. C. S., f, 63. Angina pectoris due to coronary heart disease. Following the "2-step" exercise the RS-T segments in Leads I, II and IV became depressed and returned to normal in 8 minutes. On breathing 10 per cent oxygen for 20 minutes exactly the same changes were produced proving that the electrocardiographic abnormalities after the "2-step" exercise were due to anoxemia.

minutes. Relief is frequently obtained by removing the exciting cause, usually effort. The pain may be of the classical agonizing constricting type described by Heberden with radiation down the left arm, but much more often it is a vague sensation of weight or oppression over the heart, or occasionally a choking or catching in the throat. There may be, but usually is not, pallor and perspiration. The pain is relieved by nitroglycerine. Signs of shock are usually absent. Vomiting does not occur and changes in heart sounds, heart failure, arrhythmias, and a drop in blood pressure are absent. In fact, the blood pressure may rise or remain unchanged. The electrocardiogram may remain unaltered or reveal very transient depression of the RS–T interval or inversion of the T-waves.

"Acute coronary insufficiency" [13, 14, 17] is a syndrome of a more severe myocardial ischemia than angina pectoris and is associated with myocardial damage. It is associated with a precipitating factor which decreases coronary flow or which increases the work of the heart and oxygen requirement of the heart muscle. The precipitating factors are those that bring on an ordinary attack of angina pectoris but also include tachycardia, heart failure, heart block, acute hemorrhage, shock, acute abdominal conditions, trauma, pulmonary embolism, acute cor pulmonale and hypertensive crises, aortic stenosis, syphilitic coronary arteritis, operations and infections. The syndrome of "acute coronary insufficiency" is most frequently found in the presence of coronary sclerosis but may be seen with perfectly normal coronary vessels as in aortic stenosis or insufficiency or in severe hemorrhage in a young person.[18]

Although the attack of acute coronary insufficiency may and does simulate that of complete closure of a coronary vessel, the severity of the lesion is usually less and the signs and symptoms are usually much less pronounced than one sees in coronary occlusion. Pain and shock may be absent. Heart failure, loss of intensity of the first heart sound, gallop rhythm, cardiac irregularities, and fall in blood pressure are much less common than in coronary occlusion. The lungs may be congested. Leukocytosis, fever and increased sedimentation rate are usually present to some degree. Sudden death may take place. In fact, sudden death following excitement or exertion is often the result of myocardial necrosis or infarction without occlusion.[15, 19, 20, 21, 22]

The pathological lesion in coronary insufficiency is a focal disseminated necrosis in the subendocardium and papillary muscles but no occlusion. There is usually no large, through and through infarct, from endocardium to myocardium, as one sees in coronary occlusion. That is why no mural thromboses with embolism, or pericarditis is found.

Coronary insufficiency has a characteristic electrocardiogram, namely, depression of the RS–T segments and T-wave inversions. These abnormalities occur in all leads but most frequently in Leads I and II. The changes usually return to normal fairly rapidly, sometimes in but a day or two (figure 3).

"Coronary occlusion" or thrombosis with myocardial infarction is a very characteristic syndrome presenting also a specific electrocardiographic and anatomic picture. It is a complete occlusion of a coronary vessel by a thrombus, forming directly in the intima but more commonly on the basis of an intimal hemorrhage into a sclerotic plaque with hematoma into the vessel wall and secondary thrombosis on the injured intima.[23, 24, 25, 26, 27, 28, 29, 30, 31]

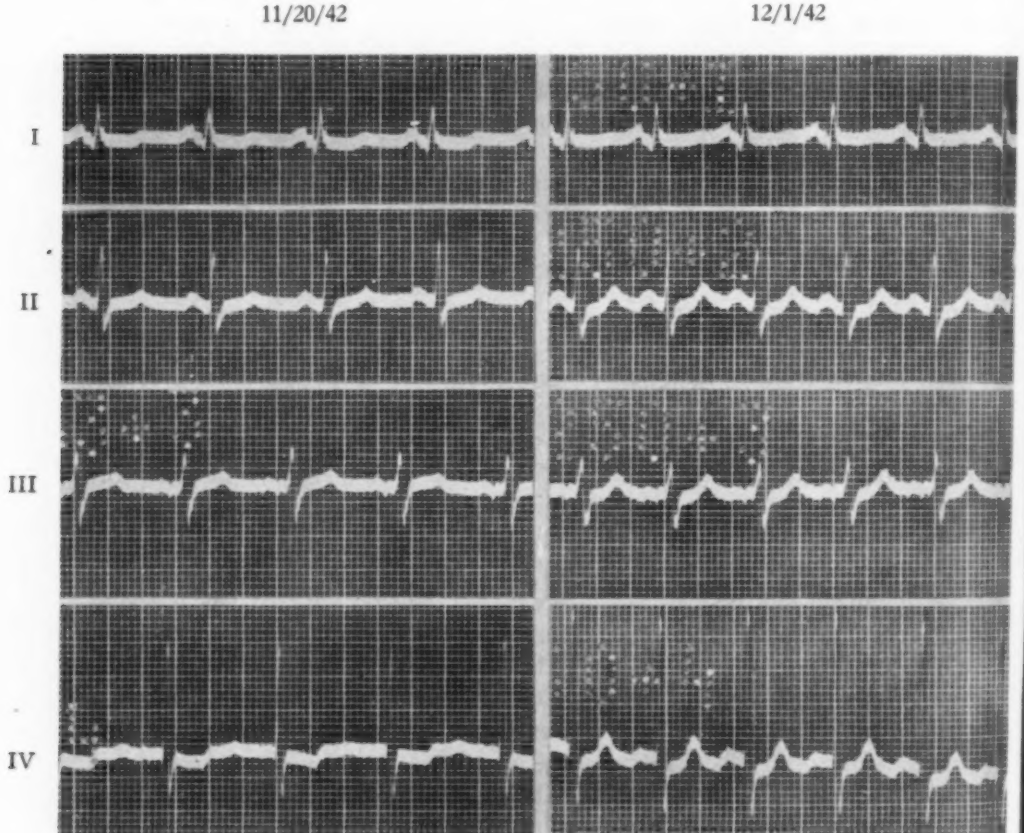

FIG. 3. L. W. McH., m, 57. Hypertensive and coronary heart disease with attacks of severe chest pain. Post-mortem revealed large left ventricle, myocardial scarring and severe sclerosis but no occlusion of the coronary arteries. Electrocardiograms showed depressions of RS–T in all leads; semi-inverted or isoelectric T_1 and inverted T_4. No digitalis.

Thus, coronary occlusion is a better term than thrombosis. A confluent massive infarct, extending from endocardium to pericardium, is observed at postmortem examination. The involvement of the endocardium explains the frequency of a mural thrombus and embolism on one hand, and the extension to the pericardium explains the pericarditis and rub on the other.

Coronary occlusion is an end result of long standing coronary sclerosis, usually is preceded by premonitory symptoms but is completely uninfluenced

by external factors, such as effort and excitement.[32, 33, 34, 35, 36, 37] In fact, this is a point of differential diagnosis from acute coronary insufficiency. The majority of attacks of coronary occlusion occur at rest or during sleep. The pain is usually much more prolonged than that of angina pectoris and may persist for hours in spite of the administration of morphine. It is unaffected or may even be aggravated by nitroglycerine. The latter will increase the tendency to shock. Shock is almost a sine qua non of coronary

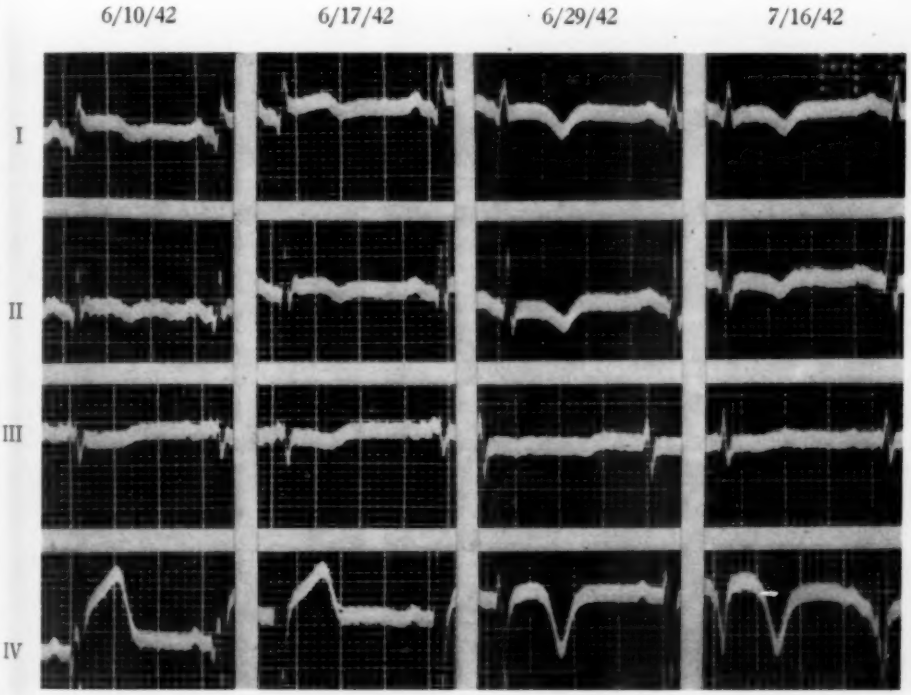

FIG. 4. A. A. G., m, 52. Coronary artery occlusion. Electrocardiogram revealed elevations RS–T segments in Leads I and IV and large Q-waves in these leads—all indicative of anterior wall infarction. RS–T elevations progressed into T-wave inversions and there was a reciprocal relationship between Leads I and III, that is, elevated RS–T I and depressed RS–T III, inverted T_1 and upright T_3.

occlusion. Gastrointestinal symptoms, such as nausea and vomiting, are very common. The blood pressure invariably falls. A change in heart sounds is a cardinal sign of acute coronary occlusion. That is, there is a reduction in the intensity of the first sound at the apex. A gallop rhythm may be heard and a pericardial rub is occasionally present. Left heart failure is very common. Leukocytosis, fever, a rapid sedimentation rate are practically always observed. The patient requires bed rest of from four to eight weeks; a gradual rehabilitation then follows.

The electrocardiogram in coronary occlusion is indeed a specific one. RS–T elevations appear which progress into deeply inverted T-waves. Deep

Q-waves are the earliest changes to be seen and the last to disappear. There is a reciprocal relationship between the RS–T and T-wave changes in Leads I and III. The abnormalities just described are seen in Leads I and IV in anterior wall infarction of the left ventricle (figure 4) and Leads II and III in posterior wall infarction (figure 5). The electrocardiographic pattern takes about four weeks to reach its stable form, i.e., deep Q-waves and

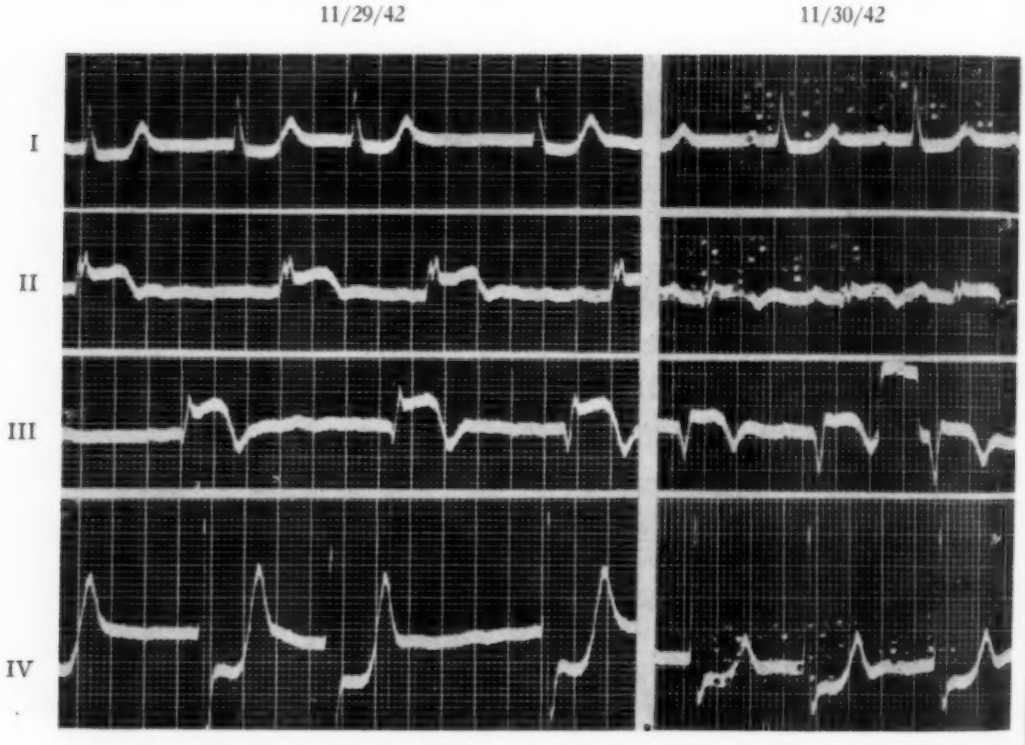

FIG. 5. C. K., m, 63. Coronary artery occlusion. Electrocardiogram disclosed fibrillation 11/29/42 but the signs of posterior wall infarction were elevations of the RS–T segments in Leads II and III with depression in Leads IV and large Q_2 and Q_3. The RS-T elevations progressed into T-wave inversions. A reciprocal relationship between Leads I and III existed, that is, elevated RS–T and depressed RS–T_1, inverted T_3 and upright T_1.

Post-mortem 12/4/42 revealed a fresh occlusion in the left circumflex artery with a large infarct in the posterior wall of the left ventricle.

T-wave inversions, and then begins to regress slightly and in 10 per cent of patients will return completely to normal by the end of the third month to the end of the first year. However, the majority of patients reveal tell-tale signs of previous coronary occlusion for years. The electrocardiogram we have described is specific and if observed will indicate coronary occlusion with infarction in 95 per cent of postmortem examinations.[14, 38]

It is thus seen that the terms angina pectoris, acute coronary insufficiency and coronary occlusion are definite clinical entities and in the last two conditions definite pathological and electrocardiographic pictures are obtained.

Current usage makes it desirable to retain these terms. The expression coronary insufficiency, as we have defined it, originated with the Germans who early recognized the entity and have described it voluminously.[39, 40, 41, 42] In the last few years Americans have taken up the expression "acute coronary insufficiency" and found it very valuable.[17, 43, 44, 45, 46, 47, 48] We have had considerable experience with cases of coronary heart disease and have found the term "coronary insufficiency" and "coronary occlusion" most helpful.[13, 14, 17]

The matter of terminology is not an academic one. An attack of angina pectoris or an episode of coronary insufficiency, i.e., necrosis or infarction of the heart muscle without occlusion of a coronary vessel, is precipitated by effort and is compensable, whereas coronary occlusion is an end result of a definite pattern of arteriosclerosis uninfluenced by events in the external environment. Over a period of many years there has been a controversy as to the question of effort, excitement and trauma precipitating coronary occlusion. It is felt that the difference of opinion would disappear if there was a common terminology in coronary disease. A plea is therefore made for this, and the suggestion voiced that the expressions angina pectoris, acute coronary insufficiency, and coronary occlusion be retained in their original and commonly accepted meanings and in the same sense that pioneer German and American clinicians and pathologists have used these terms.

Recently there has been an endeavor to avoid specific terminology in coronary heart disease when there is definite injury of the heart muscle, and to use the broad term myocardial infarction without any qualifications. This is avoiding the issue and only makes for confusion of thought. If the term is used at all it should be qualified; thus, "myocardial infarction with coronary occlusion" or "myocardial infarction without coronary occlusion." However, the term coronary occlusion should be retained. There is nothing in medicine more specific, clinically, pathologically or electrocardiographically, and it is as easy to make the diagnosis of this disease as it is to make the diagnosis of acute appendicitis or lobar pneumonia.

Conclusion

With the increasing span of life, coronary heart disease has taken a preeminent position since the turn of the century. It is an ubiquitous disease and spares neither the sedentary person, laborer, the soldier nor sailor. It is the chief cause of death in this country.

The terms "angina pectoris" due to coronary disease, "acute coronary insufficiency" are specific and should be retained. Their diagnoses are simple to make clinically. Coronary insufficiency has a characteristic picture and coronary occlusion actually possesses a pathognomonic, pathological and electrocardiographic pattern.

Angina pectoris due to coronary disease is a transitory attack of anterior chest pain, precipitated by exertion, emotion, cold, trauma, ingestion of food,

etc., and relieved by nitroglycerine. It is due to a temporary ischemia and is not accompanied by any pathological change in myocardium.

"Acute coronary insufficiency" is usually associated with a precipitating factor, such as that which causes an ordinary attack of angina pectoris, but also is observed in tachycardia, heart failure, acute hemorrhage, operation, shock, aortic stenosis and insufficiency, syphilitic coronary ostitis, etc., which reduce the coronary flow or increase the work of the heart and the oxygen requirement of the heart muscle. If the ischemia is severe and prolonged, focal, disseminated necrosis in the subendocardium and the bases of the papillary muscles will result. A depression of the RS–T segment and T-wave inversions are characteristic.

Coronary occlusion or thrombosis occurs irrespective of external factors except possibly operation and shock. Shock, nausea and vomiting, a fall in blood pressure, distant heart sounds, left heart failure, fever, leukocytosis, and rapid sedimentation rate are practically always found. A gallop rhythm and a pericardial rub may be heard. The pathological and electrocardiographic findings are specific. A confluent massive infarct extends from endocardium to pericardium, thus frequently giving rise to embolism and pericarditis. The electrocardiogram discloses RS–T elevations (which progress into T-wave inversions), deep Q-waves, and a reciprocal relationship of the RS–T and T-wave changes in Leads I and III.

Military personnel, more than civilians, do not appreciate the omnipresence of coronary heart disease. This disease should be ruled out in all officers and men over 30 years of age and it is suggested that a test for latent coronary insufficiency, such as the "electrocardiogram" and the "2-step," be used.

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SMALL INTESTINAL DISORDERS IN AVITAMINOSIS *

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ALTHOUGH the small intestine constitutes the greatest part of the gastrointestinal tract, it has not received the attention one might expect. The lack of clinical information regarding the small bowel is striking despite the fact that many gastrointestinal symptoms have their origin in disturbed motility of this organ. The principal reason for this is the rarity with which organic lesions affect the small intestine, duodenal ulcer and regional enteritis excepted. Further, although other parts of the gastrointestinal tract can be visualized directly, examination of the small bowel is confined largely to roentgen study.

Recent renewed interest in the small intestine is due principally to evidence that variations in motility may occur secondary to certain vitamin deficiencies. In addition functional changes may occur which disturb the absorption of essential food factors.

There is considerable evidence that the vitamins are intimately concerned with gastrointestinal function. McCarrison [1] fed monkeys on an autoclaved rice diet, and noted that digestive symptoms were the first to occur. Loss of appetite and depraved appetite were prominent, and vomiting occurred occasionally. Diarrhea was found to be the most important as well as the most constant symptom. McCarrison believed these disturbances due to degeneration of the nerves of the myenteric plexuses. Golden [31] has recently revived this concept. Gross [2] noted hypermotility of the intestinal tract of rats as a result of vitamin A deficiency, and hypomotility in vitamin B deficiency. Plummer [3] found that absence of vitamin B from the diet of rats diminished the length of time during which an excised strip of small bowel exhibited spontaneous contractions in oxygenated Locke's solution. Crandall [4] noted the appearance of a "deficiency pattern" roentgenographically in the small bowel of dogs placed on a black tongue producing diet, and found that in several animals this abnormal intestinal pattern appeared before black tongue. Heublein [5] found a tendency to hypertonicity early in the acute phase of vitamin B deficiency in dogs. Later other changes were noted, some atonic in type. Following crystalline vitamin B_1 administration there was a temporary return to normal motility, but complete restitution to normal did not occur until whole yeast was given by mouth. Martin et al.[6] found that inositol markedly increased the peristaltic action of the stomach and small intestine in dogs, and that nicotinic acid decreased peristalsis. They

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suggested that the balance or ratio of nicotinic acid or similar compounds to inositol is the nutritional factor which determines hypo- or hypermotility. The same authors [7] later concluded that inositol and pantothenic acid were the constituents of the vitamin B complex associated with the maintenance of normal gastrointestinal motility.

Experimental data in man are meager. It has long been known that anorexia is a prominent symptom of vitamin B deficiency. Elsom et al.[8] maintained a patient on a diet deficient in the vitamin B complex and noted mild anorexia after one week, which ultimately became extreme. Heartburn, epigastric fullness, and distention were other symptoms suggesting disturbed motility. Later, nausea, vomiting, and moderately severe generalized abdominal pain appeared. Thiamine chloride administration was followed by return of appetite, but after two weeks anorexia again appeared which was not relieved until yeast was given. Williams and his coworkers [9] noted that capricious appetite, indigestion, distention, eructation, nausea, vomiting, constipation or diarrhea, and mucous colitis were characteristic of induced thiamine deficiency in man. Crandall [4] studied a group of patients with symptoms of abdominal distress, flatulence, constipation alternating with diarrhea, and anorexia, in whom the diagnosis of functional gastrointestinal disease had been made. An appreciable number were improved after the administration of nicotinic acid, and a greater number after taking a preparation of the vitamin B complex. There was no alleviation of symptoms after the administration of thiamine chloride or riboflavin.

There is recent evidence that deficiency states are accompanied not only by disturbed gastrointestinal motility, but also by defective absorption. Groen,[10] by means of a simplified technic of intestinal intubation, studied the glucose absorption of 10 patients with various dietary deficiency diseases. As compared with normal controls, there were three cases of pernicious anemia and one case of "alcoholic" polyneuritis with pellagra which demonstrated diminished absorption of glucose before treatment. Absorption of glucose returned to normal after adequate treatment. In these patients the blood sugar rose less during the absorption test than it did in controls. This appears to be a reasonable explanation for the flat glucose tolerance test seen in the sprue syndrome and occasionally in other deficiency states. There is evidence [11] that the addition of vitamin B complex in the form of whole yeast to a diet considered adequate will cause hastened digestion and absorption of carbohydrate. Addition of individual components of the vitamin B complex has no such effect (thiamine chloride, nicotinic acid, pyridoxine). The effects of yeast may be due to other factors such as inositol or pantothenic acid, or to actual excitation of the secretory cells of the small bowel and stomach.[9, 12, 13]

That fats are inadequately absorbed in certain deficiency states is indicated by the steatorrhea that occurs in the sprue syndrome.

Zetzel et al.,[14] employing the same method as Groen, demonstrated that

patients with chronic ulcerative colitis accompanied by deficiency disease are unable to absorb an amino acid mixture from the upper jejunum to a degree comparable with normal individuals.

FIG. 1. Normal roentgen appearance of the upper small intestine.

With the above evidence in mind, it is possible that in vitamin deficiency states there is defective absorption of essential food factors and vitamins, and that a vicious cycle is thus instituted.

The first important application of the roentgen-ray in the diagnosis of a functional small intestinal disturbance was not reported until almost four decades after the initial use of the opaque meal.[15] This is an index of the difficulties which surround roentgen investigation in this field. Until about 1930 clinical examination was carried out almost solely to find or exclude neoplasms or gross inflammatory lesions. The typical "normal" roentgen

picture of the small bowel was defined earlier, particularly by Cole and those working with him.[16] In order to study functional changes it was found necessary to standardize technics and eliminate foodstuffs from the opaque meal.[17, 18] The method now generally employed is to give a suspension of four ounces of barium sulfate in an equal amount of water in the morning after an overnight fast. The progress of the meal is then followed by frequent roentgenograms or fluoroscopic examinations or both, until most of the meal has entered the cecum (usually four to six hours). The normal duodenum and jejunum show a feathery fenestrated appearance due to the infiltration of the barium suspension into the complicated and changing pattern of the mucosal folds (figure 1). The barium column tends to be continuous and of uniform caliber. However, Morse and Cole [16] have called attention to the variations in caliber and distribution of the meal with intermittent and irregular emptying of the stomach; the extent to which this factor contributes to the abnormal patterns to be described subsequently, has as yet not been evaluated. In the ileum there is more tendency for the barium to collect in boluses, and here the mucosal folds are low or absent. Wherever active contractions are occurring, parallel longitudinal folds are outlined.

In 1933 Mackie reported a case of non-tropical sprue with distinctive roentgen changes in the small bowel.[19] Subsequently he and others amplified the description of the findings and established them as a constant feature of the sprue syndrome.[20, 21, 22, 23, 24] It was shown that the severity of the changes is roughly proportional to the clinical severity, and that return toward normal occurs with clinical improvement. There is marked disturbance of motility with accumulation of quantities of the opaque material in loops that appear dilated and smooth. This appearance has been described as the "moulage" effect.[22] Between such loops are segments empty of barium giving the impression that areas of reduced tonus alternate with spastic ones. This impression is strengthened when such a case is studied fluoroscopically, for one can observe relative inactivity and stasis in these dilated segments for long periods. The deviations from normal are most obvious in the duodenum and jejunum, and indeed may be confined to these portions of the intestine. A striking feature of the more advanced cases is the presence of gas and fluid levels in the dilated loops simulating intestinal obstruction. Snell and Camp [20] described associated dilatation and redundancy of the colon, and Kantor [22] considered idiopathic steatorrhea to be the sole serious chronic diarrhea in which a dilated instead of a spastic colon may be found. A comparable small bowel roentgen picture has been described in children suffering from celiac disease.[25] Zwerling and Nelson [26] have recently noted wide variations in the small bowel roentgen pattern in 77 presumably normal infants and children. So-called normal "adult" patterns were distinctly rare and occurred in only five of the 77 children. So-called "deficiency" patterns were observed in 38 infants and children. This in-

dicates that the small bowel roentgen picture cannot be relied upon as an index of vitamin B complex deficiency in infants and young children until more complete studies of the factors which influence the pattern in individuals of this age group have been obtained.

The concept that non-tropical sprue might be a deficiency disease was considered as early as 1917 by Elders (quoted by Mackie [19]). Since then this has been repeatedly emphasized. It remained to be shown that functional changes in the small bowel as determined by barium meal study might occur in other deficiency states. This second important phase in the development of our present concepts of small bowel physiology in deficiency disease began when Mackie in 1935 demonstrated similar roentgenographic changes in patients with chronic ulcerative colitis.[27] He postulated a relative insufficiency of the antineuritic vitamin as the cause of the apparent reduction in tone with depression of motility in these cases. However, other factors in the vitamin B complex have been found to play a more important rôle (vide supra). More recently Mackie and Mills [28] have reported good correlation between clinical evidence of vitamin B deficiency and roentgen findings in cases of chronic ulcerative colitis in which the latter were positive. In 1941 Lepore and Golden [29] described a syndrome which they felt was largely due to vitamin B complex deficiency, and characterized by the following: history of diet high in carbohydrate and poor in vitamin B complex, in fat and in protein, weight loss, asthenia, anorexia, faintness two to four hours after meals, flatulence, diffuse abdominal pain, constipation or diarrhea, malnutrition, hypochlorhydria or achlorhydria, increased capillary fragility, and flat oral glucose tolerance curve. Patients presenting this symptom complex had an abnormal small bowel pattern, and return to normal occurred after administration of vitamin B complex by mouth and parenterally, and crude liver extract parenterally. Golden [30, 31] stressed the importance of recognizing the roentgen changes, particularly the milder ones, and did much to arouse the interest of roentgenologists in the problem. He characterizes the "deficiency pattern" as follows: with respect to motility, hypermotility and hypertonicity are seen early, hypomotility and dilatation in advanced cases; abnormal segmentation is the rule; with respect to the mucosa there is coarsening or obliteration of the pattern and flocculation of the barium.

Pathological verification of the changes visualized by roentgenograms is scant, and necessarily refers chiefly to the graver affections, especially cases of the sprue syndrome terminating fatally. In one such case [22] a dilated jejunum with thinned pouched areas was found, the thinned areas being devoid of valvulae conniventes. Histologic findings in the small bowel in deficiency states are not distinctive, the most consistent characteristics being edema of the submucosa and round cell infiltration.[31]

Below are described two cases which illustrate the roentgenologic changes of deficiency states as described above. The first patient presented mild

changes which improved following therapy. The second demonstrated severe changes which were apparently irreversible. The clinical picture in the latter patient approximated in some respects that seen in the sprue syndrome.

Case Reports

Case 1. Mrs. A. B., 67 years old, was admitted on Dr. C. L. Brown's service on September 19, 1941, following an attack of acute left ventricular failure. Physical examination was not remarkable except for marked obesity (235 pounds), left ventricular enlargement, blood pressure 205 mm. Hg systolic and 105 mm. diastolic, and vitiligo of the hands. There was no clinical evidence of vitamin deficiency. The electrocardiogram and orthodiagram substantiated the clinical impression of left ventricular enlargement and strain. The patient was digitalized and a reduction diet of 1,000 calories per 24 hours, containing 70 gm. protein, was prescribed. She was discharged improved on October 11, 1941. The patient was readmitted on November 16, 1941 with complaints of distaste for food and nausea. She had been overconscientious in adherence to the diet, and had lost 20 pounds. There had been no vomiting nor diarrhea; in fact, she had become quite constipated. She also complained of flatulence. Physical examination revealed no new findings. Gastrointestinal roentgen study disclosed the "deficiency pattern" (figure 2). She was unable to tolerate yeast or yeast extracts so that a "syrup of vitamins" containing 5 mg. thiamine chloride, 25 mg. nicotinamide, 3 mg. riboflavin, 25 mg. pyridoxine per drachm was prescribed, two drachms three times daily. In addition she received 50 mg. of thiamine chloride and 100 mg. nicotinamide intramuscularly daily and parenteral liver extract, 15 U.S.P. units three times weekly for two weeks. Her appetite improved, nausea disappeared, and she was discharged on December 14, 1941. The "syrup of vitamins" was continued. In June of 1942 she returned weighing 186 pounds and feeling well. Roentgen study revealed improvement in the small bowel pattern (figure 3).

*Case 2.** Mr. C. H., 43 years old, was admitted on Dr. Brown's service on August 14, 1942 with chief complaints of pain and weakness of the legs and intermittent diarrhea of three years' duration. For 10 years he had been a traveling salesman, and because of a dislike for restaurant foods had sharply curtailed his diet. An analysis of his daily food intake disclosed marked deficiency in all the vitamins and calcium. Three years prior to admission he developed pain in his legs and ankles which gradually increased in severity. Two years prior to admission he began to have bulky, foul, fatty stools, which recurred at intervals. At the same time there occurred several severe nose bleeds, hematuria, and bleeding of the gums. A diagnosis of scurvy was made, and he was treated with ascorbic acid. Improvement was very slow. The hemorrhagic manifestations finally disappeared but the other symptoms persisted. Physical examination revealed malnutrition, bronze colored skin, normal heart and lungs, blood pressure 100 mm. Hg systolic and 60 mm. diastolic, distention of the abdomen, enlarged tender ankles and slight non-pitting edema of the legs. Laboratory studies disclosed a mild hypochromic anemia, prothrombin time 28 seconds (control 15.5 seconds), serum calcium 7.0 mg./100 c.c., serum phosphorus 2.43 mg./100 c.c., phosphatase 14.1 Bodansky units, serum protein 5.0 gm./100 c.c.

* Since this article was submitted for publication additional information has become available concerning case 2 (C. H.). The patient was re-admitted one year later with more severe bone pain and epigastric distress. He progressed downhill after discharge and died in another hospital. Autopsy showed, in addition to mild chronic inflammatory changes throughout the bowel, eight fibrotic annular constrictions of the proximal jejunum about six centimeters apart responsible for a high degree of obstruction. No clue as to the etiology of these constrictions was provided by their histologic appearance.

(albumin 3.92 gm./100 c.c., globulin 1.08/100 c.c.), blood vitamin C level 0.71 mg./100 c.c. Gastric analysis disclosed normal free HCl and total acidity. Roentgenograms of knees, ankles, skull and spine revealed marked osteoporosis. Roentgen study of the small bowel on August 22, 1942 disclosed an extreme example of the "deficiency pattern" (figure 4). Despite adequate therapy which included large

FIG. 2. *Case 1* (before treatment). Roentgenogram showing "deficiency pattern" of moderate degree.

doses of thiamine chloride, nicotinamide, pyridoxine, riboflavin by mouth and parenterally, brewers' yeast, calcium salts by mouth and parenterally, high protein diet, plasma transfusions and crude liver extract intramuscularly, a second small bowel roentgen study on November 11, 1942 revealed no improvement. There was no clinical improvement nor return to normal of the blood chemistry.

Snell and Camp [20] and Golden [31] indicated that the roentgenologic changes are non-specific. That gastrointestinal allergy may produce disturbed in-

testinal motility, demonstrable by roentgenographic study, has been noted.[32, 33, 34, 35] Emotional disturbances may produce similar disturbances.[31] Hypocalcemia may likewise affect the small bowel pattern.[36] Pendergrass et al.[18] described disturbed intestinal motility in diabetes insipidus and in nephrosis. It has been demonstrated[37] that a reduction in the concentration of serum

FIG. 3. *Case 1* (after treatment). Roentgenogram showing return toward normal.

proteins in dogs is associated with marked reduction of passage of the barium meal through the small bowel and clumping of the barium. These abnormal alterations were corrected by restoring serum protein to a normal level by diet or transfusions of lyophilized plasma. Golden suggests that edema of the mucosal or submucosal layers may be the common denominator in the production of these changes.[31] However, we have recently seen one patient in the nephrotic stage of glomerulonephritis with anasarca and a serum protein

level of 3.7 gm. per 100 c.c. who had a small intestinal pattern within normal limits. Patients with portal cirrhosis, obstructive jaundice, or with metastatic peritoneal carcinoma may show an abnormal pattern.

FIG. 4. *Case 2.* Roentgenogram demonstrating "deficiency changes" of severe degree in duodenum and jejunum.

SUMMARY

There is experimental evidence in animals that gastrointestinal motility and absorption depend to some extent on vitamins, notably certain members of the vitamin B complex. There is evidence that such is the case in man. Lack of these vitamins may result in changes which are early reversible, but later become irreversible.

The small bowel roentgenographic "deficiency pattern" is characterized by hypermotility and hypertonicity early, hypomotility and dilatation in ad-

vanced cases. Abnormal segmentation is the rule. Coarsening or obliteration of the mucosal pattern and flocculation of the barium occur.

There are limitations to the dependability of the deficiency pattern as a criterion for the diagnosis of vitamin B complex deficiency. If the roentgenologic changes are mild they cannot be distinguished from normal variations since no extended series of complete "small intestinal studies" in normal individuals has been published. In addition it is possible that modifications in the pattern of the same patient may occur from time to time, depending on other factors, for example emotional disturbances. Further, recent work has indicated that the healthy child may normally show a "deficiency pattern."

This confusion should not cause the abandonment of this method of study, but should stimulate an attempt at a more extensive appraisal with an effort to correlate functional roentgenographic findings with other physiologic methods. During this period of careful evaluation patients with "functional" gastrointestinal disturbances who demonstrate the roentgenographic changes in the small bowel pattern deserve a trial of vitamin B therapy. This should be in the form of yeast by mouth and crude liver extract parenterally. Supplemental use of other individual components of the B complex may be of value.

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CASE REPORTS

METASTATIC GRANULOMA VENEREUM; REPORT OF A CASE *

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Granuloma venereum (granuloma inguinale) is a chronic infectious disease, usually transmitted by sexual contact, characterized in most cases by ulcerative and granulomatous lesions of the genitalia or adjacent regions. It was first reported in 1882 by McLeod,[1] in India, and was described more completely in 1896 by Conyers and Daniels,[2] who observed the disease in South America. In 1904 Donovan,[3] who studied granuloma inguinale in India, described the inclusion bodies which are characteristic of the disease and which bear his name.

Subsequent to the earlier reports, cases of granuloma inguinale have been described in all of the great continents and in many sub-continents and smaller islands. Though most prevalent in tropical and subtropical climates, it is not rare in the temperate zones. It was first reported in the United States by Grindon[4] in 1913; during the 1920's hundreds of cases were reported from nearly all sections of the country.[5, 6, 7, 8, 9, 10, 11] It is quite common in the Southern states, and patients with this disease are constantly present on the Contagious Service of the Charity Hospital.

The incidence of granuloma inguinale is much higher in negroes than in white persons, and it is apparently more common in males than in females. It is certain, however, that many cases in women have escaped recognition because of the location of lesions in the vagina or upon the cervix. Its highest age incidence is between 20 and 40, but it has been reported in a man of 94,[12] a child of 6,[13] and even in a newborn baby.[14]

The disease seems usually to be transmitted by sexual contact, but undoubted instances of nonvenereal infection have been reported,[15, 16] and some observers[16] doubt that granuloma inguinale is a venereal disease. The incubation period has not been determined, estimates varying between two days and several months.

The earliest lesion is a small papule which usually appears upon or near the genitalia—the penis, vulva, vagina, cervix uteri, groin, or perineum. Ulceration soon occurs; the ulcer slowly spreads peripherally and after several months may attain enormous size, extending upward upon the abdomen, downward upon the thighs, and backward upon the buttocks. Most commonly ulceration is superficial but occasionally it extends deeply into the tissues. Complete destruction of the penis is not rare. Lesions upon the cervix are usually fungating in type,[17] bleed easily, and have been confounded with carcinoma. The course of the disease is exceedingly chronic, extending over a period of years, with little

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or no tendency toward complete spontaneous healing, though remissions, during which reëpitheliazation and scarring occur, are the rule.

Smears from the lesions, stained with Wright, Giemsa, or Dieterle's (silver) stains, constantly show the characteristic Donovan bodies within large monocytic

FIG. 1. Appearance of lesions one week after admission. Note swelling in and below right breast.

cells (figure 5). These cells with their inclusion bodies constitute the characteristic feature of biopsies as well.[18] The nature of the Donovan bodies is not known. They have been considered to be protozoa, and the cause of the disease, but some observers have mentioned the possibility of their being fungi. Attempts to cultivate them in artificial media have been generally unsuccessful.

Extragenital lesions, though unusual, are not at all rare. In most instances such lesions follow genital or pudendal lesions, and are presumably due to contact infection, but primary extragenital lesions have been known to occur.[10, 12, 15, 19] Sites of extragenital lesions include the mouth and lips [12, 20, 22, 23, 25, 27, 29, 31] (observed rather frequently), cheek,[21] nose,[22] neck,[12, 22, 23, 24, 25] throat,[22, 31] back of hand,[26] lower portion of the thigh,[20] and at the site of a skin graft.[8]

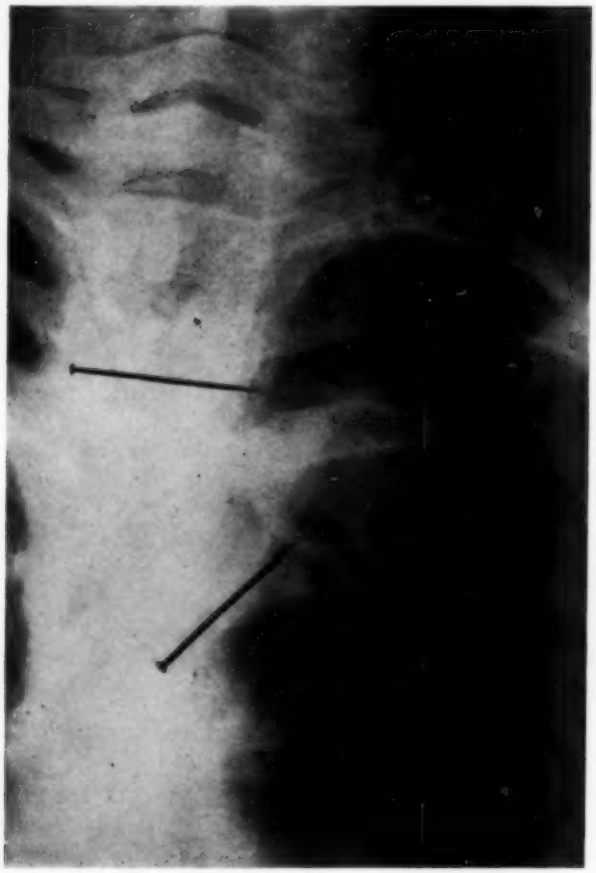

FIG. 2. Lesions in left clavicle.

Involvement of internal organs is decidedly rare, and in nearly all instances has been the result of direct extension of lesions of the skin or mucous membranes. Stricture may follow involvement of the anal canal[28]; rarely the process extends higher in the colon.[12, 28] Extension to the fallopian tubes and ovaries has occurred.[30] Lesions of the larynx and pharynx have been reported.[12, 25, 31]

Systemic symptoms are slight or absent in granuloma venereum unless secondary infection, deep ulceration, rectal stricture, or extension to tubes and ovaries has occurred. The lesions responded slowly but definitely to therapy with anti-

mony compounds (first employed by Aragão and Vianna [32]). Although complete healing often takes place during treatment, relapse is common after seemingly adequate therapy.

Case Report

E. C., a 21 year old negress, began, in mid-October of 1942, to have dull pain in the upper sternal region and on either side of it. The pain appeared following a trivial injury. There was tenderness in the same regions, and the pain was increased

Fig. 3. Lesion in rib.

by turning of the head. Over a period of two or three weeks pain and tenderness increased in severity, and fever, malaise, and drenching night sweats appeared. During this same period a vaginal discharge, at first mucoid and later mucopurulent, was noted.

By mid-November, two walnut-sized swellings had developed, one over the medial end of each clavicle. These masses softened, and the skin overlying them became thin and reddened. One of the lesions was squeezed by a friend, with the release of a thin bloody material. On the next day a deep open ulcer with everted edges was present. Within a few days the other lesion ruptured spontaneously

forming an ulcer similar to the first. The two lesions increased in size and became confluent, forming a deep, large, irregular ulcer. The vaginal discharge meanwhile had become more profuse and bloody, fever and malaise persisted, and progressive weakness occurred.

Late in December a lesion similar to the first two appeared below the right breast. This lesion remained firm in consistency, but attained the size of half an orange. About a week later pain appeared in the left infraaxillary region, and soon thereafter a mass developed in that location. This lesion gradually softened but did not rupture. Later a lesion appeared in the left groin, which ruptured spontaneously, forming a deep ulcer.

FIG. 4. Lesion in scapula.

In February 1943 painful swelling of the left labium majus, followed shortly by ulceration, occurred. During this month another painful subcutaneous swelling was noted in the right scapular region. Constitutional symptoms became more severe, marked weakness was present, and considerable weight loss had occurred during the four months which had elapsed between the onset of her illness and her admission to the Charity Hospital on February 25, 1943.

Upon admission, the patient was acutely ill, febrile, emaciated, and somewhat delirious. Six cutaneous and subcutaneous lesions were present: (1) in the upper sternal region over the medial ends of the clavicles, (2) beneath the right breast, (3) in the left infraaxillary region near the midaxillary line, (4) over the right scapula near its inner border, (5) in the left groin, (6) on the left labium majus.

The lesions in the sternal region and the groin consisted of deep ulcers with dark red, moist, granulomatous floors which bled upon touch, and with indurated crusted borders (figure 1).

The lesions beneath the right breast and over the right scapula were tender, firm but cystic, and the skin overlying them was intact. The left infraaxillary lesion was soft and fluctuant, the overlying skin thin and erythematous.

The labial lesion consisted of a deep ulcer which occupied the lower half of the inner surface, surrounded by an area of brawny swelling. Upon the cervix uteri

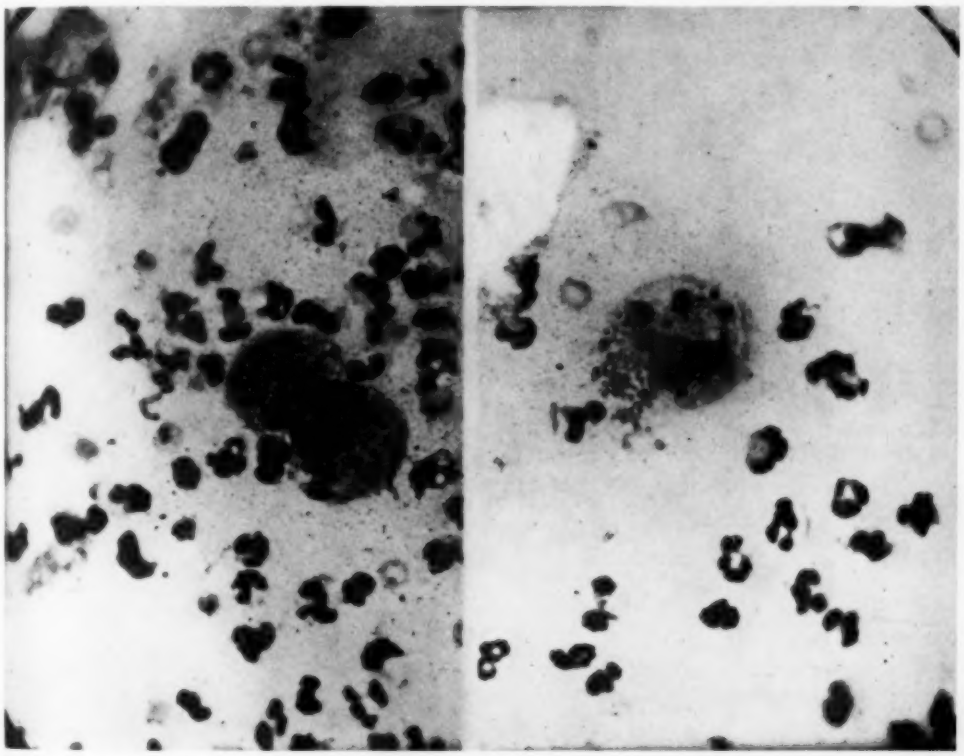

FIG. 5. Donovan bodies in smear from excised lesion of right sixth rib.

there was a large fungating mass which bled copiously upon the slightest touch. No adnexal masses were felt, but satisfactory bimanual examination was impossible because of marked tenderness of the vulva.

No signs of disease of the thoracic or abdominal viscera were present. Blood pressure was 124 mm. Hg systolic and 78 mm. diastolic.

Moderate anemia (red blood cells 3.6 million, hemoglobin 8.9 grams) and leukocytosis (14,000) were present. The urine contained granular casts and pus cells in moderate numbers. Blood Kline and Kolmer tests were negative. Blood cultures showed no growth. Coccidioidin and tuberculin skin tests were negative. Serum proteins and blood urea were normal.

Roentgenograms showed osteolytic lesions in the medial end of the left clavicle (figure 2), the anterior portion of the right sixth rib (figure 3), the axillary portion of the left tenth rib, and the medial portion of the right scapula (figure 4). A roentgenogram of the chest showed no evidence of lung disease.

Donovan bodies were abundantly demonstrable in all of the ulcerative lesions (sternal region, groin, labium majus, cervix). Aspiration of the fluctuant mass in the left infraaxillary region yielded thin serosanguinous fluid which contained enormous numbers of Donovan bodies, but no bacteria nor fungi upon smear and culture. Shortly after aspiration sloughing of the skin overlying this lesion occurred,

FIG. 6. Appearance of lesion shortly before discharge. Light material is iodoform powder.

producing a deep ulcer similar to those in other locations. Biopsy material from this ulcer and those of the sternal region and groin, and from the cervical lesion as well, showed the characteristic lesions of granuloma venereum.

In order to obtain biopsy material in a region where the skin was unbroken, the lesion below the right breast, together with the underlying portion of the sixth rib, was excised, the operative wound surprisingly healing by primary intention. Char-

acteristic pathologic lesions of granuloma venereum were demonstrable in the rib (figure 5), subcutaneous tissue, and skin. (The pathologic findings are to be reported in detail by Palik and Schenken.)

Pending establishment of the diagnosis, sulfathiazole was employed in full dosage and two blood transfusions were given. Improvement in the general condition of the patient had occurred prior to the beginning of specific therapy, but the lesions continued unchanged, and fever, ranging as high as 103° F., was present every day.

On March 8, 1943, twelve days after admission, therapy with Diramin * was begun; injections were given at five day intervals after that date. The initial dose was 1 c.c., followed by gradual increase to 5 c.c.

Systemic and local improvement began almost immediately but progressed slowly. The temperature declined gradually and remained normal after April 8. The ulcerative lesions gradually diminished in depth and diameter. The lesion of the scapular region did not ulcerate, and resolved completely. Gain in weight and strength occurred gradually.

The patient had been ambulatory for one month before her discharge from the hospital on May 24, 1943. At this time the ulcers of the groin and sternal region were less than half of their former diameters, and their floors were almost level with the surrounding skin (figure 6). The lesion of the infraaxillary region was almost completely healed. The labial lesion had decreased in size, and the edema which formerly surrounded it had disappeared. The lesion of the cervix uteri was greatly diminished in size and no longer bled. The bone defects were practically unchanged.

Treatment of the patient with Diramin was continued in the out patient department. No toxic effects of the drug were observed.

Discussion

It appears that in this patient the initial lesion occurred upon the cervix uteri, and that for a time this lesion produced no symptoms. Much later the disease spread to the left labium majus. It seems likely that the lesion of the left groin, although present before the labial lesion was noticed by the patient, was due to extension via the lymphatics from a small unnoticed lesion of the labium majus. The great depth of the ulceration of the groin from its incipiency and the presence of swelling before the occurrence of ulceration preclude the possibility of this lesion's being due to contact of the skin with infectious material.

It is certain that the lesions upon the anterior, posterior, and lateral surfaces of the chest were not due to contact of the skin of these regions with infectious material. These lesions first appeared as subcutaneous swellings covered by unbroken skin. Lesions were demonstrable in bones which lay beneath the subcutaneous lesions, in the absence of ulceration of the skin. Donovan bodies were abundantly present in fluid aspirated through unbroken skin, and in bone which was involved in the absence of a gross lesion of the superjacent skin. It must be concluded that the infectious agent reached these parts remote from the initial lesion via the blood stream, and it appears highly probable that the metastatic lesions began in the clavicle, ribs, and scapula and pointed toward the surface after destruction of bone had taken place.

* A trivalent antimony compound supplied us by Parke, Davis and Company for investigational purposes. One c.c. of the solution contains 8.5 mg. of antimony.

Summary

A case of granuloma venereum with metastatic lesions of the left clavicle, right scapula, right sixth rib, and left tenth rib is reported. Subcutaneous abscesses, two of which were followed by deep ulcers, occurred over each of the sites of bone involvement. The initial lesion involved the cervix uteri and spread to involve the vulva. Ulceration of the left groin, considered to be the result of lymphatic spread from the vulval lesion, was also present, but the metastatic lesions appeared before involvement of the vulva and groin. Constitutional symptoms, usually slight or absent in cases of granuloma venereum, were very severe. Marked improvement of the lesions and disappearance of the constitutional symptoms followed therapy with Diramin, a trivalent antimony compound.

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CHRONIC GLOMERULONEPHRITIS FOR FORTY YEARS: REPORT OF CASE *

By Norman M. Keith, M.D., Howard M. Odel, M.D., F.A.C.P., and Archie H. Baggenstoss, M.D., *Rochester, Minnesota*

The course of chronic glomerulonephritis has been a subject of interest since Bright [1] considered it in a paper published in 1840. His appraisal of the course was necessarily limited to a period of 10 to 15 years; however, Mann [2] in 1895 reported a case which he had followed for 28 years. Recently two factors have stimulated a renewed interest in the subject. The first is that clinicians have made a more intensive application of physiologic principles to the immediate problem of the patient and their findings created a desire for the second factor, namely, an accurate record of the whole course of the patient's illness. In the last few years several groups of physicians have published detailed observations made during the course of chronic Bright's disease. These include the reports of Van Slyke and his co-workers,[3] Addis and Oliver,[4] Volhard and Suter,[5] and Ellis.[6] All are agreed that some patients who have chronic glomerulonephritis can live comfortably for many years and a few even for several decades. Our patient belongs to the latter group and we believe her course is unique because continuous observations were made in the same institution over a period of 40 years.

* The patient was presented before a clinic on glomerulonephritis at the annual meeting of the American College of Physicians, St. Paul, Minnesota, April 23, 1942.

Case Report

The patient, an unmarried woman, visited the Mayo Clinic periodically during the past 40 years. Her first visit was at the age of 17 years. Renal disease had begun the previous summer, that of 1901, when edema of the legs developed insidiously. Her face also became puffy, the urine scanty, and the patient experienced loss of appetite and general weakness. She first consulted a physician at the clinic on January 21, 1902. At that visit the edema was noted and routine urinalysis disclosed

Table I

Certain Clinical Data

Date	Blood Pressure, mm. of Mercury	Edema, Grade	Retinitis, Grade	Hemoglobin, gm. in 100 c.c. of Blood	Urine		
					Albumin, Grade	Casts, Grade	Erythrocytes, Grade
1–21–02		3			4	3	
4–15–02		2			4	2	
4– 6–11		0–1			Trace	0	
9–22–13		0–1			1	0	
12– 6–13	155/120	0–1					
4–14–14	130/90	0–1			Trace	0	
9– 4–15	125	0–1			0	0	
4–26–27	180/110	2		70*	4	2	Occ.
7– 4–28	140/90	1		55*	2–4	0	Occ.
6– 2–30	145/90	0–1			2	0	Occ.
3–10–32	145/95	1		12.3**	4	1	1
5–19–33	150/95	1		10.7**	4	1	0
1–15–35	170/110	0–1	1†	7.9**	4	1	0
9–30–35	170/105	1		9.5**	3	0	0
10–30–36	180/115	1		10.5**	3	0	1
8–10–39	210/120	1		10.5	3	0	0
10–29–40	190/100	0–1			3	0	Occ.
3–25–41	180/105	0–1		9.6	3	0	0
1–22–42	185/100	0–1			3	1	0
4–14–42	190/110	1		9.8**	4	0	0
8–15–42	205/130	2	1†	10.0	4	0	Occ.
9–18–42	150/100	3‡	1		4	0	0
9–20–42§							

* Dare method of estimation of hemoglobin.

** Same values for hemoglobin are dated one or two days earlier or later than in table 2.

† Date of ophthalmologic examinations seven days earlier and two days later than days listed.

‡ Concentration of protein in urine 1.09 gm. in 100 c.c.

§ Patient died.

abundant albumin and casts. The patient was seen again on April 15, 1902, and appeared to be much better. There was less edema, but the urine still contained albumin and casts (table 1). She gradually improved and had very little trouble with edema for many years.

On April 6, 1911, the patient returned to the clinic because of enlarged lymph nodes in the left side of the neck. Resection was performed on April 7 and again on July 1, 1911; the condition was found by the pathologist to be tuberculous. At

this time the routine urinalysis revealed a trace of albumin. In 1913 at the age of 28, her complaint on visiting the clinic was headaches. The blood pressure was determined for the first time and the systolic pressure was found to be 145 mm. of mercury and diastolic 115 mm. Albumin, grade 1, was present in the urine (grading is on a basis of 1 to 4 in which 1 designates the mildest and 4 the severest condition). On further estimations in 1913 the systolic blood pressure was found to vary between 140 and 155 mm. of mercury and the diastolic between 115 and 120 mm. During the years 1914 and 1915 the patient was examined on three occasions. Because of infected tonsils, tonsillectomy was performed on October 2, 1915. The blood pressure readings during these two years were 125 to 130 mm. of mercury systolic and 90 mm. diastolic, which were essentially normal values. Urinalysis revealed the presence of a trace of albumin on two occasions while on a third no albumin was present. The sediment in all three analyses was free from casts and blood cells. Thus the record of this patient revealed a normal blood pressure and normal urine on routine analysis on one or more occasions 14 years after the onset of glomerulonephritis. The patient's disease was evidently in a latent phase (table 1).

Following tonsillectomy in 1915 the patient continued to have good health for approximately 10 years. Occasionally she noticed some edema of the lower part of the legs, but with rest and elevation of the legs it would soon disappear. In 1926, however, she began to have persistent edema of legs and hands with dyspnea on exertion and attacks of vertigo. These symptoms gradually grew worse and 11 months after their onset she sought medical advice at the clinic.

On examination April 26, 1927, at the age of 43 years, the patient weighed 145 pounds (66 kg.), her normal weight being 115 pounds (52.3 kg.). On examination of the mouth her teeth appeared in good condition. There was no gross pyorrhea. Dental roentgenograms revealed one root, number 17, and one tooth, number 7, with possible periapical infection. The blood pressures were 180 mm. of mercury systolic and 110 mm. diastolic. The peripheral arteries seemed perhaps slightly thickened on palpation. There were no objective signs of cardiac abnormalities and examination of the ocular fundi did not disclose any definite sclerosis of the retinal arterioles. Generalized edema, which was grade 1, of the face and grade 2 of the lower extremities, was present. The urine contained albumin, grade 1 to 4, and at times the sediment revealed a moderate number of hyaline casts and a few erythrocytes and leukocytes. A concentration test of the urine revealed a maximal specific gravity of 1.024. From 60 to 80 per cent of the phenolsulfonphthalein injected was excreted in two hours. Examination of the blood revealed erythrocytes 4,680,000 per cubic millimeter, leukocytes 5,600, and a concentration of hemoglobin of 70 per cent (Dare method). The flocculation test in serum for syphilis was negative. The concentrations of urea and creatinine in whole blood were 14 and 1.3 mg. respectively in 100 c.c. The concentration of chlorides in the plasma was 595 mg. in 100 c.c., the carbon dioxide combining power of the plasma was normal, 60 volumes per cent, but the concentration of protein in the serum was reduced to 5.1 mg. in 100 c.c. (table 2). An electrocardiogram revealed a sinus tachycardia with essentially normal tracings. Such findings clearly indicated the recurrence of a nephrotic phase during the course of chronic glomerulonephritis. The patient received hospital treatment for a period of 32 days. This consisted of a weighed diet which contained 1,500 calories, 40 gm. of protein and a low content of sodium chloride and water. The intake of extra fluid was limited to 600 to 1,200 c.c. daily. The administration of drugs included 132 gm. of ammonium nitrate and four injections of salyrgan (6.5 c.c.). The output of urine varied from 500 to 2,500 c.c. per day. The patient lost 29½ pounds (13.4 kg.) and practically all of the edema disappeared. With loss of edema fluid the blood pressures decreased from 180 mm. of mercury systolic and 110 mm. diastolic to 90 mm. systolic and 60 mm. diastolic. During the dehydration treatment the concentration

of urea in the blood increased to 62 mg. in 100 c.c., but decreased to 40 mg. before the patient left the hospital. This increase in blood urea has occurred frequently in our experience when combined diuretic measures are employed in such cases. However, subsequent to dismissal from the hospital the concentration of urea in the blood often is found to be normal as it was in the present case (table 2). On dismissal the patient was instructed to continue the same diet, to ingest 800 c.c. of extra fluid and 4 gm. of ammonium nitrate daily.

TABLE II

Chemical Studies in the Blood

Date	Whole Blood			Plasma			Serum			
	Hemoglobin gm. in 100 c.c.	Urea, mg. in 100 c.c.	Creatinine, mg. in 100 c.c.	Chloride, mg. in 100 c.c.	CO_2 combining power, volume per cent	Cholesterol, mg. in 100 c.c.	Protein, gm. in 100 c.c.	Albumin, gm. in 100 c.c.	A/G ratio	Sulfate, mg. in 100 c.c.
5- 2-27		14	1.3	595	60		5.1			
5-14-27		62	1.4	535	48					
5-28-27		40								
6- 2-27							5.9	2.7	0.8/1	
3-14-28		28					6.2	3.1	1/1	
7- 6-28		28								
6- 3-30		26				252	7.3			
3-11-32	12.3*	30				326	6.5	2.2	0.5/1	5.8
5-20-33	10.7*	40								8.4
10- 7-33		56								8.5
1-16-35	7.9*	84	3.1				7.6	2.7	0.5/1	8.2
10- 1-35	9.5*	84	3.0							8.8
10-28-36	10.5*	118	5.4							9.8
8-10-39	10.5	68	2.3				7.9	3.95	1/1	8.5
10-30-40		72								10.4
3-25-41	9.6	96	3.9				6.8	3.4	1/1	14.4
1-21-42		92	3.4				6.8	3.2	0.9/1	13.4
4-15-42	9.8*	88	4.0		37					
8-15-42	10.0	138	8.4	611	27					
8-18-42		154	9.6	569	36		5.5	2.4	0.8/1	
8-24-42		204	10.4	519	34					10.1
8-29-42		242	9.6	519	45					
9-18-42		182	9.9	495	47	264				
9-20-42†										

* The same values for hemoglobin are dated one to two days earlier or later than in table 1.
† Patient died.

During the next three years the patient had several examinations. The peripheral edema never disappeared entirely but was readily controlled. The patient's strict adherence to the diet, low in salts and fluid, was undoubtedly helpful in limiting the edema. The blood pressure remained within normal limits and the concentration of albumin in the urine varied from grade 1 to 4. Renal functional tests revealed normal output of phenolsulfonphthalein, normal concentration of urea in the blood and a rise in serum protein to 7.3 gm. in 100 c.c. During the spring of 1928 varicose veins with thrombophlebitis in the legs and a moderate secondary anemia developed. Both internal saphenous veins were ligated, the varicose veins were excised on August 7, 1928, and by the end of the month of treatment the anemia had disappeared. Evidently the renal disease was for the second time in a latent phase (tables 1 and 2).

In June, 1930, a checkup, including roentgenograms of the thorax and sinuses of the head, was made; these roentgenograms revealed nothing abnormal.

From June, 1930, until February, 1932, we did not see the patient. She had gotten along quite satisfactorily and had adhered to a diet low in protein, sodium chloride and fluids. On her return for a checkup on March 10, 1932, although anemia was not present and neither the edema nor hypertension was marked, the blood pressures being 145 mm. of mercury systolic and 95 mm. diastolic, there was evidence of increasing renal insufficiency. The urine contained albumin, grade 4, considerable numbers of hyaline and granular casts, erythrocytes and leukocytes and the serum sulfate had increased to 5.8 mg. in 100 c.c.[7] The serum protein was still 6.5 gm. in 100 c.c. but the serum albumin had decreased to 2.2 gm. The concentration of cholesterol was 326 mg. in 100 c.c. of plasma, a value distinctly higher than the normal. Thus at this stage of the patient's disease renal function was impaired and the serum proteins and lipoids were definitely abnormal (tables 1 and 2).

A year later in May, 1933, several findings indicated further progression of the disease. The blood pressures were 150 mm. of mercury systolic and 95 mm. diastolic. The concentration of hemoglobin in the blood was 10.7 gm. in 100 c.c. and albuminuria of grade 4 was present. The output of phenolsulfonphthalein had fallen to 40 per cent in one hour, the concentration of sulfate in serum had increased to 8.4 mg. in 100 c.c. and both the urea and sulfate clearances were abnormally decreased to 23 and 12 c.c. respectively per minute. Treatment at this time consisted of a diet low in protein (40 to 50 gm.), low in sodium chloride and a somewhat more liberal intake of fluid (1,200 to 1,500 c.c.). From May, 1933, until the death of the patient in September, 1942 (nine years and four months), chronic renal insufficiency of considerable degree was readily demonstrable (tables 1 and 2). For approximately nine of these years the extent of renal impairment did not increase markedly, but considerable fluctuation in renal function occurred from time to time. Evidence of marked and progressive renal failure was present only during the last month of the patient's life (table 2).

It is of interest that this considerable impairment of renal function was present for two years, 1933 and 1934, before definite involvement of the cardiovascular system occurred. At the end of this period in January, 1935, the blood pressures had risen to 170 mm. of mercury systolic and 110 mm. diastolic. Auscultation over the heart revealed a distinct accentuation of the second aortic sound; on palpation the peripheral arteries were thickened and ophthalmoscopic examination revealed some narrowing of the retinal arterioles. All of these abnormal cardiovascular findings persisted until the patient's death seven and a half years later.

The discovery of retinitis on January 8, 1935, is of interest. The ophthalmoscopic examination revealed slight narrowing and thickening of the retinal arterioles, one cotton-wool patch and a small hemorrhage in the left retina. The optic disks appeared paler than normal. The concentration of hemoglobin in the blood at that time was reduced to 7.9 gm. in 100 c.c. and Dr. H. P. Wagener interpreted the retinitis as being due to anemia rather than to vascular alterations.[8] Two months later, March, 1935, the retinitis had entirely cleared up and did not recur for a period of seven and a half years or until August, 1942 (table 1).

Repeated examinations during the interval of six and a half years, from October, 1935, until April, 1942, revealed little if any progress in the different components of the disease. The extent of the hypertension was similar on the two dates. The extent of the edema of the lower part of the legs had increased slightly and weight had increased 5 pounds (2.3 kg.). The concentrations of hemoglobin and urea in the blood were approximately the same on both dates, although the concentration of creatinine had increased slightly from 3.0 to 4.0 mg. in 100 c.c. Another interesting

fact was that an electrocardiogram taken on January 22, 1942, differed little from the normal (figure 1). During this entire period of six and a half years the patient had always been able to walk from her home to the clinic. She also had carried out her own housework and gone about town in a normal manner. In April, 1942, she was quite capable of enjoying an auto ride of about 160 miles without fatigue.

The therapeutic measures stressed during the period from October, 1935, to April, 1942, were a diet consisting of approximately 2,000 calories, 60 gm. of protein, 4 gm. of sodium chloride, and 2,000 c.c. of extra fluid. Because of the moderate secondary anemia, iron in the form of citrate or sulfate was given in considerable doses throughout the entire period. The results of the administration of iron to this patient

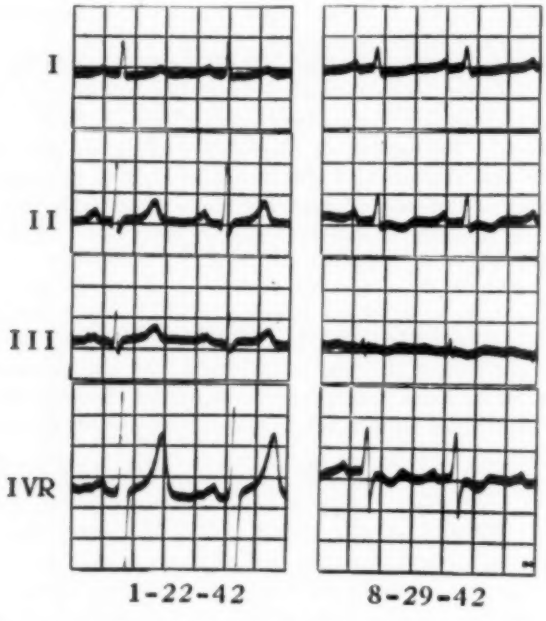

FIG. 1. Essentially normal electrocardiogram taken January 22, 1942. Electrocardiogram taken August 29, 1942, reveals iso-electric, diphasic or inverted T-waves in all leads.

and to other patients in a similar stage of chronic glomerulonephritis indicate that iron can be helpful in arresting an otherwise progressive anemia.

During the month, April 14 to May 13, 1942, the patient carried on much as usual and enjoyed the spring weather. Then on May 14 cough, fever and distress deep in her thorax developed. Because of the persistence and increasing severity of the cough and pain in the thorax the patient returned to the clinic and entered the hospital on August 15. From May 14 until her death four months later the patient continued to show signs of progressive myocardial failure, increasing dyspnea, dependent edema, pulmonary and hepatic congestion and bilateral hydrothorax. The final complication was the occurrence of an acute pericarditis. During the terminal period of cardiac failure, on August 29, the electrocardiogram definitely indicated deterioration of myocardial function (figure 1). At this time mild retinitis also developed. On August 17 Dr. H. P. Wagener noted slight general narrowing and thickening and an occasional suggestion of postspastic sclerosis of the retinal arterioles, moderate arteriolosclerosis of some choroidal vessels, a few cotton-wool

exudates in each retina with one hemorrhage in the right. He was of the opinion that the retinitis was of the angiospastic type.[8] It will be recalled that the retinitis present for a few months in 1935 was considered to be secondary to anemia. The treatment of the patient's myocardial failure included the use of digitalis, the xanthine compounds, theocalcin and aminophylline, and repeated paracentesis of both pleural cavities. Oxygen also was administered periodically from September 6 to 19.

During the last four months of the patient's illness, myocardial failure was associated with a considerable degree of hypertension, the blood pressure rising to higher levels than at any previous period (table 1). Myocardial failure was also accompanied by considerable proteinuria of 1 per cent and a gradual increase in renal insufficiency until it became marked: the blood urea increased to 242 mg. in 100 c.c., the creatinine to 10.4 mg. in 100 c.c. and the carbon dioxide combining power of the plasma decreased to 27 volumes per cent (tables 1 and 2). However, the renal retention of metabolites in the blood, that is, urea and creatinine, and the degree of acidosis present did not reach the extreme degrees sometimes observed in the terminal stage of chronic glomerulonephritis. It should be pointed out that the

TABLE III

Chemical Studies in Blood Plasma and Serum during Terminal Phase of Patient's Illness

Date 1942	Plasma		Serum				
	Chloride, mg. in 100 c.c.	Carbon Dioxide Combining Power, volume per cent	Sodium, mg. in 100 c.c.	Potassium, mg. in 100 c.c.	Calcium, mg. in 100 c.c.	Sulfate, mg. in 100 c.c.	Phosphorus, mg. in 100 c.c.
8-18	569	36	296	22.7	7.2		8.6
8-24	519	34				10.1	
8-29	519	45	285	21.6			
9-18	495	47		22.6			

acidosis was controlled by the administration of sodium bicarbonate. The changes observed in the concentration of certain inorganic ions in the plasma and serum of this patient are characteristic of chronic uremia; these are a decrease in the concentration of chloride, sodium and calcium and an increase in the concentration of sulfate and phosphate (tables 2 and 3). The concentration of potassium was slightly increased. The mental status of the patient during the last month was also of interest. Apparently at times she became mentally confused for a few minutes but did not lapse into coma until the last 24 hours. In fact she was able to carry on a sensible conversation until a day or two before death.

PATHOLOGIC FINDINGS

Anatomic Findings. The body measured 162 cm. in length and was estimated to weigh 140 pounds (63.6 kg.). Severe subcutaneous edema extended from the lower extremities up to the level of the umbilicus. The right pleural cavity contained 1,200 c.c. of clear fluid with flakes of fibrin and the left pleural cavity contained 1,000 c.c. of a similar fluid. There were a few fibrous adhesions at the apex of each lung. The transverse diameter of the pericardium was 18 cm. and the pericardial sac contained 300 c.c. of bloodstained fluid. The pericardium was thickened and firm fibrous adhesions extended from the apex of the left ventricle to the parietal pericardium.

The heart weighed 500 gm. and was covered by a hemorrhagic fibrinous exudate

(figure 2). The left ventricle was greatly hypertrophied. At the base of the posterior leaflet of the mitral valve, just within the left auricle, there was a small (3 mm. in diameter) calcified nodule to which a soft thrombus which measured 5 by 9 mm. was attached. The coronary sclerosis was graded 2+ (on the grading basis of 1 to 4).

The lungs were not remarkable grossly except for moderate atelectasis and congestion of both lower lobes. The spleen was much atrophied and weighed only

FIG. 2. Heart; fibrinous pericarditis with a fibrous pericardial adhesion at the apex.

18 gm. (figure 3*a*). There was a moderate hyaline perisplenitis and the consistency was greatly increased. The cut surface was brown and the follicles were indistinct. The scrapings were greatly decreased. There was a number of superficial ulcerations of the mucosa of the duodenum but the remainder of the gastrointestinal tract was normal.

The right kidney weighed 61 gm. The capsule was stripped with moderate difficulty from a coarsely granular, brownish yellow surface (figure 3*b*). The con-

sistency was increased. There were numerous pitted scars and a number of small cortical cysts which measured approximately 1 mm. in diameter. The cut surface was yellowish brown and the normal markings were slightly indistinct. The cortex was narrow and its thickness averaged 0.4 cm. The medulla was 0.9 cm. in depth. The pelvis, calices and ureter appeared normal. The left kidney weighed 63 gm. and had essentially the same appearance as the right one. The aortic sclerosis was severe throughout the entire aorta but atheromatous and calcified plaques were most numerous in the abdominal portion.

The brain weighed 1,201 gm. There was a mild degree of flattening of the convolutions and slight arteriosclerosis of the basilar vessels but otherwise the brain appeared grossly normal.

The posterior half of each eye was removed. There were numerous tiny exudates in the retinas of both eyes. There was a small (2 mm.) hemorrhage in the retina of the right eye.

FIG. 3*a*. Atrophy of the spleen; spleen weighed only 18 gm. A spleen of normal size weighing 150 gm. is shown for comparison. *b*. Atrophy and scarring of kidneys; kidneys weighed 124 gm.; normal weight of kidneys is 300 gm.

Histologic Examination. The most significant lesions were present in the kidneys, heart and brain.

In the kidney all the glomeruli examined revealed evidence of injury in varying degrees. The majority of the glomeruli were hyalinized, obviously functionless structures associated with atrophied tubules (figures 4 and 5*a*). In some glomeruli only a portion of the capillary tuft was hyalinized and the walls of the remaining capillaries were thickened and had a hyaline appearance. The capsules of the damaged glomeruli were generally thickened with hyaline connective tissue. Other glomeruli revealed an increase in the number of endothelial nuclei and thickening of the capillary basement membranes. The capillaries, however, were patent and contained erythrocytes (figure 5*b*). These glomeruli, which apparently were still functional, were usually increased in size. Connected with such glomeruli were dilated tubules which often contained albuminous casts and occasional polymorphonuclear leukocytes. Hyaline granular degeneration was frequently present in the lining cells of the convoluted tubules. The interstitial tissue contained many lymphocytes and increased numbers of fibroblasts and connective tissue. In the

FIG. 4. Chronic glomerulonephritis (hematoxylin and eosin × 15).

arteries of the kidney there was elastic intimal thickening of varying degree but in general the walls were markedly thickened (figure 6). The arterioles revealed hypertrophy of the media and hyaline thickening of the intima of moderate degree (figure 7*a*).

On the adipose connective tissue of the epicardium there was a very vascular granulation tissue. This granulation tissue consisted of newly formed capillaries, actively proliferating fibroblasts, some lymphocytes and a few polymorphonuclear

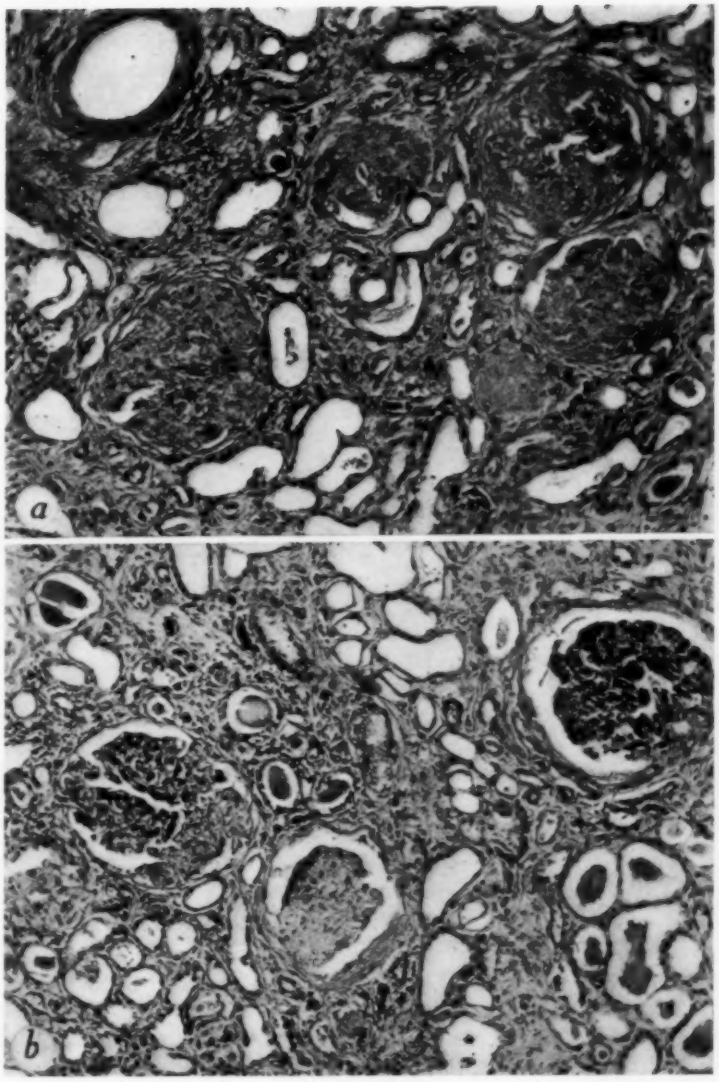

FIG. 5. Chronic glomerulonephritis; *a*, hyalinization of glomeruli; dilatation of tubules with atrophy of lining epithelium (hematoxylin and eosin × 85); *b*, another section (hematoxylin and eosin × 80).

leukocytes. There were occasional larger collections of polymorphonuclear leukocytes within the granulation tissue. Superimposed on the surface of the organizing granulation tissue was a more recent fibrinopurulent exudate.

The parietal pericardium had an appearance similar to that of the epicardium. At the base of the posterior leaflet of the mitral valve was a deposit of calcium which was surrounded by lymphocytes, large mononuclear cells and a few polymorphonuclear leukocytes. There was some proliferation of fibroblasts also. A small thrombus was attached to the endocardium over the calcium deposit.

The myocardium revealed hypertrophy of the muscle fibers as well as a slight

increase of loose interstitial connective tissue. Moderate fatty metamorphosis was present in many muscle fibers in sections from both ventricles and from the interventricular septum. Many of the muscle fibers were fragmented.

The arterioles of the brain revealed a moderate degree of hyaline thickening of the intima in all sections that were taken. There were also minute infarcts in the cortex and medulla, in which there was necrosis and degeneration of nerve cells together with glial proliferation. Vessels in the vicinity of these lesions were not obstructed, however.

There were minute collections of apparently recent albuminous exudate in both retinas in addition to the small hemorrhage which was described grossly. Mild edema of the optic disks, as revealed by separation of the nerve bundles, was observed. There were mild sclerosis of the retinal arterioles and moderate sclerosis of the arterioles of the choroid coat of the eyes (figure *7b*).

In the spleen hyaline arteriosclerosis and arteriolosclerosis were severe. The

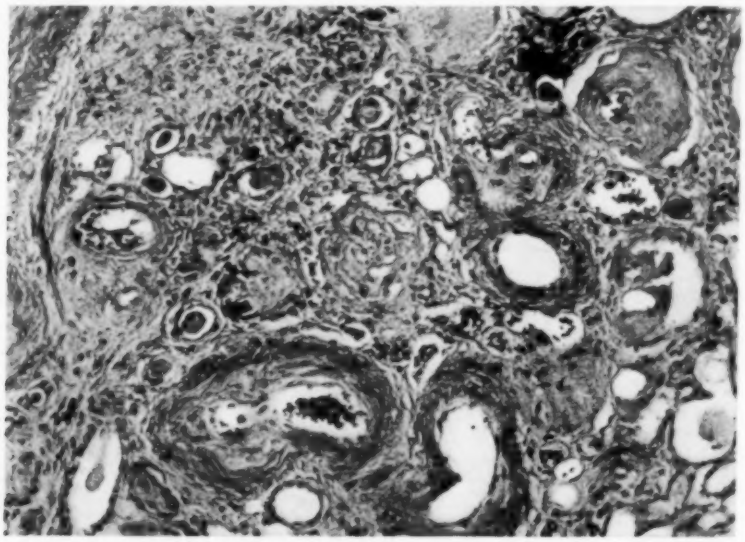

FIG. 6. Elastic intimal thickening of arteries of kidney (hematoxylin and eosin × 100).

lymphatic nodules were absent and cellular elements from the pulp had disappeared. The capsule and the trabeculae were thickened greatly by fibrous connective tissue. Deposits of brown pigment in the capsule and trabeculae were shown to consist of iron by appropriate stains.

Mild chronic passive congestion of the liver and moderate arteriolosclerosis were present. The latter consisted of medial hypertrophy in some arterioles and of hyaline thickening of the intima in others. Similar arteriolar changes also were noted in the adrenal glands, pancreas and gall-bladder.

The following anatomic diagnoses were made: chronic glomerulonephritis with atrophy of kidneys; hypertrophy of the heart (hypertension); organizing fibrinopurulent pericarditis with fibrous adhesions at the apex of the left ventricle; miliary infarcts of brain; exudative retinitis; bilateral hydrothorax with atelectasis of lower lobes of lungs; fatty metamorphosis of myocardium; focal calcification of mitral ring; atrophy of spleen; edema of legs; arteriosclerosis of aorta, grade 3; arteriolosclerosis of the kidneys, adrenal glands, liver, spleen, pancreas, brain, retinas and choroid coats of the eyes.

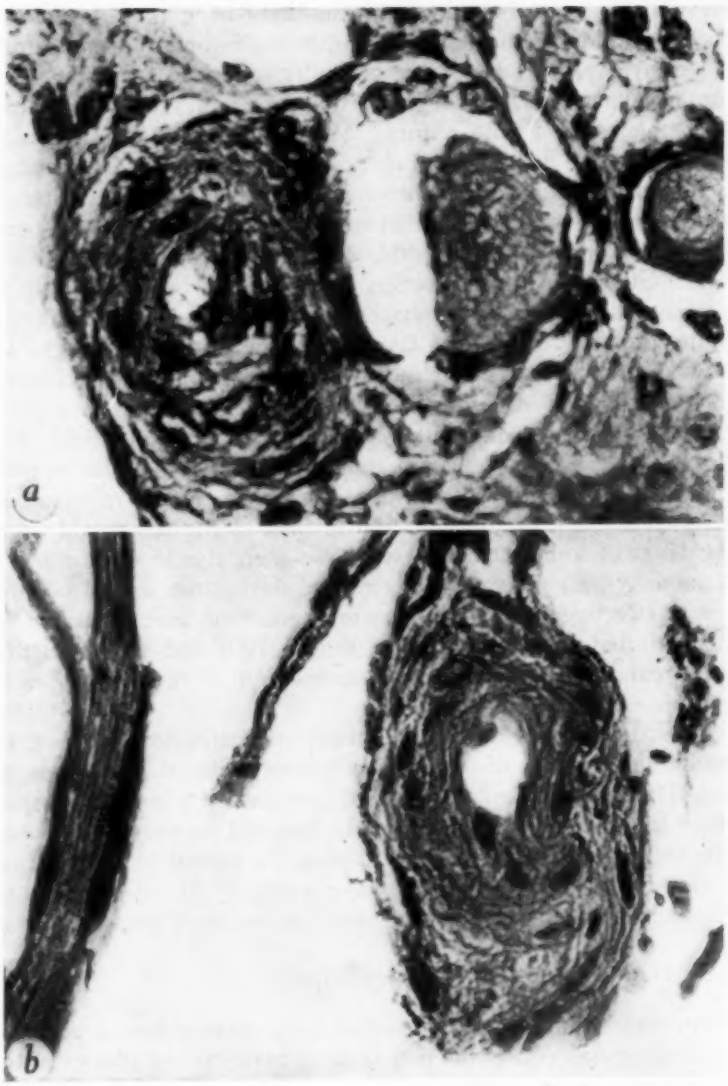

FIG. 7. Arteriolosclerosis; *a*, of kidney (hematoxylin and eosin × 515); *b*, of choroid coat of the eye (hematoxylin and eosin × 515).

COMMENT

The story of this patient's illness might suggest that she had suffered from different types of glomerulonephritis. The long course of her illness can be divided into six distinct phases as follows: (1) an initial nephrotic episode; (2) a latent phase of approximately 23 years; (3) a second nephrotic episode; (4) a second latent phase of three years; (5) a period of slowly developing renal insufficiency and hypertension lasting 10 years; (6) a short terminal phase of myocardial failure. Such a record of events favors the concept that there

is a basic underlying pathologic factor in cases of glomerulonephritis, which under certain conditions may give rise to a nephrotic syndrome, under others to a hypertensive vascular syndrome or under others to a combination of both.

The multiple manifestations of glomerulonephritis revealed in our case remind us of its complex and diffuse nature. When general edema was a prominent symptom, there were definite disturbances of protein and fat metabolism; for example, hypoproteinemia and hypercholesterolemia. On the other hand, diffuse cardiovascular phenomena varied from a mild symptomless hypertension to such serious developments as retinitis, myocardial hypertrophy and failure, and pericarditis. Studies of renal function were of value in determining the extent of renal damage during different phases of the disease. They were also helpful in estimating the effect of a given therapeutic agent on the damaged kidney.

It is always difficult to evaluate methods of therapy in cases of chronic disease; nevertheless, it does seem probable that our patient's long and thorough cooperation with her physicians with regard to diet, intake of fluid, ingestion of iron and avoidance of unnecessary exposure to changes in the weather was of distinct help. We can only ask the question, was there any relation between the long continued anemia, or the ingestion of iron to the remarkably small spleen (weighing 18 gm.) found at necropsy? We wish also to draw attention to the fact that the dehydration treatment employed during the second nephrotic phase in 1927 was effective in a much shorter period of time than the method of treatment instituted in the initial phase during 1901 and 1902, and that the use of diuretic agents such as salyrgan and ammonium nitrate in 1927 did not have a lasting toxic effect.

It is noteworthy that patients who have nephritis accommodate themselves to a considerable degree of renal insufficiency without symptoms of general disability. This was particularly true of our patient for many years. In fact she received treatment for nephritis in the hospital on only two occasions, once in 1927 to reduce edema and in 1942 during the period of terminal myocardial failure. In other words, our patient was chronically ill for 40 years, but during most of this time was able to carry on much as a normal person.

Conclusions

The course of chronic glomerulonephritis can extend over a period of several decades. During this period the patient may have various phases of the disease, tolerate renal insufficiency satisfactorily, and live comfortably.

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EDITORIAL

PALINDROMIC RHEUMATISM

UNDER the sonorous title of palindromic (recurrent) rheumatism Hench and Rosenberg [1] have described a "new" and interesting malady which appears to be readily distinguishable from the ordinary types of arthritis. According to these authors the syndrome is characterized by brief recurring attacks of pain, swelling, tenderness and redness in or about a joint, with variable and often marked temporary disability. There is no fever or notable constitutional disturbance, and recovery is invariably complete, the joints suffering no permanent injury.

The onset of an attack was usually abrupt, the pain reaching a maximum within three hours and sometimes within half an hour. The attacks were brief, usually subsiding within one to three days, and sometimes within a few hours. Less frequently they might last for three to six days, and in two cases rarely for two to three weeks. The pain varied greatly in intensity, was often disabling and sometimes required narcotics.

In a majority of the 34 cases the attacks recurred at short intervals of about one to two weeks, but without any regularity or periodicity. In some cases they occurred almost daily, but in a few there were intervals of freedom of from one to six months. Four of the cases estimated the number of their attacks in the hundreds or even thousands. The duration of the disease at the time the patient was seen varied from less than a year to more than 20 years, with an average of seven years.

In 90 per cent of the cases only one joint was involved in a given attack, although two or several might be affected simultaneously. In subsequent attacks, however, a different joint was likely to be affected, the distribution being capricious and unpredictable. The joints most frequently involved were the fingers, including the terminal interphalangeal joints, the wrists, elbows, shoulders, knees and toes, but practically any joint in the body might be attacked.

The joint involved showed swelling, usually moderate in degree, due to effusion into the joint cavity. There was usually also localized periarticular swelling which might overshadow the intra-articular effusion. In addition, in 30 per cent of the cases there appeared localized, well demarcated swellings in the soft tissues, about 2.5 to 4 cm. in diameter, firm, red and tender, usually but not always in association with an attack of arthritis. They were not, however, necessarily near the joint involved. They were often near or somewhat proximal to one of the larger joints, or on the palms or finger pads.

[1] HENCH, P. S., and ROSENBERG, E. F.: Palindromic rheumatism: a "new" oft-recurring disease of the joints (arthritis, periarthritis, para-arthritis) apparently producing no articular residues: report of 34 cases. (Its relationship to "angioneural arthrosis," "allergic rheumatism," and rheumatoid arthritis.) Proc. Staff Meet. Mayo Clin., 1941, xvi, 808.

They usually disappeared within 24 hours. They were described as being more circumscribed, firmer, more painful and tender than areas of ordinary angioneurotic edema. In addition in three cases small subcutaneous fibroid nodules were observed.

The authors stress the absence of fever and constitutional disturbances, although pain may cause temporary disability. The usual laboratory examinations showed merely a relative lymphocytosis (37 to 49 per cent) and a moderate transient increase in sedimentation rate during an attack. There was no significant increase in total leukocyte count, no eosinophilia and no anemia.

In two cases biopsy during an attack showed a fibrinopurulent exudate in the joint cavity and an acute inflammatory reaction in the synovial membranes with many leukocytes, including neutrophiles, in the interstitial tissues and about the small blood vessels. In two cases, examined between attacks, the articular tissues were perfectly normal.

In spite of repeated attacks, no joint showed evidence of permanent injury, either clinically or roentgenographically. Of 164 roentgenograms taken, these authors reported that 150 were entirely negative and 14 showed coincidental abnormalities unrelated to the attacks. This point is well brought out by a case recently reported by Mazer.[2] In spite of hundreds of attacks over a period of 30 years, roentgenograms of the knee showed no joint changes whatsoever.

The various types of treatment employed had little if any demonstrable effect on the course of the disease. The attacks ceased in four of the 27 cases followed up, and were reduced in frequency in 12 others. In three the frequency increased, and there was no change in the remainder.

The disease is rare if the rigid criteria of the authors are observed. They collected only 34 cases at the Mayo Clinic in a period of about 13 years, during which a very large number (not precisely stated) of cases of arthritis were observed.

Cases (27 in all) resembling those of Hench and Rosenberg were reported by Solis-Cohen [3] in 1914, under the term angioneural arthroses. He described frequently recurring, usually brief attacks of pain and swelling affecting the joints, periarticular tissues or tendon sheaths, singly or in combination, together with the occasional appearance of tender lumps in the soft tissues proximal to the joints. The attacks might be monarticular, or several joints might be involved in one or more attacks. Practically any joints in the body might be affected. In a few cases a recurring hydrarthrosis was restricted to the same single joint, often the knee, but usually many different joints were involved in successive attacks, and he emphasized the "capriciousness and whimsicality" of the phenomena. He also stressed

[2] MAZER, M.: Palindromic rheumatism, Jr. Am. Med. Assoc., 1942, cxx, 364–365.

[3] SOLIS-COHEN, S.: On some angioneural arthroses (periarthroses, para-arthroses) commonly mistaken for gout or rheumatism, Am. Jr. Med. Sci., 1914, cxlvii, 228–243.

the presence of other recognized manifestations of vasomotor instability, or as he termed it, ataxia autonomica.

Solis-Cohen's cases differed from those of Hench and Rosenberg in several respects. In 40 per cent fever occurred with one or more attacks. Multiple joint involvement was much more common. The duration of some of the attacks was longer, "several weeks." Vasomotor disturbances, skin rashes and allergic phenomena were more frequent. Whether these differences are significant can be determined only by further observations. It is quite possible that the criteria set by Hench and Rosenberg may prove to be too rigid.

Kahlmeter [4] in 1939 also described a group of 54 cases which in most respects closely resembled those of Hench and Rosenberg. There were recurring brief attacks of pain and intra-articular, periarticular and para-articular swelling which might be marked in degree and was often migratory. As a rule there was no fever or evidence of local inflammation, although occasionally these were observed. The swelling usually involved only one or two joints at a time, but in successive attacks or even during the same attack, the swelling might shift its location in a capricious way. The joints showed no residual injury. Kahlmeter also noted the relative lymphocytosis, the absence of eosinophilia and transient elevation of the sedimentation rate during the attacks. The principal difference from Hench and Rosenberg's cases was the great frequency with which allergic reactions were observed, either in association with an attack of arthritis or independently. Urticaria was observed in 35 per cent, angioneurotic edema in 11 per cent, asthma in 13 per cent and migraine in 9.5 per cent. In about a quarter of the cases an attack was preceded by gastrointestinal disturbances which were thought to be allergic. Kahlmeter regarded the arthritis as allergic in origin.

Vaughn [5] has since reported a study of the arthritis found in 1,000 consecutive cases of allergic disease in adults. From 206 cases with either a clear history or clinical manifestations of arthritis, he isolated a group of 27 cases in which attacks of arthritis were precipitated by taking foods to which they were sensitive. In 20 cases the food was identified (in only half by skin tests), whereas in seven the arthritis occurred in association with other manifestations of an allergic reaction. At least 10 cases which showed no residual joint changes appear to fall into Hench and Rosenberg's group. Some of the others showed definite joint disease and appear to have been cases of real arthritis in whom an allergic reaction started an exacerbation of the process. Vaughn reported that the attacks could be relieved by withholding the offending food.

Hench and Rosenberg, on the other hand, were not impressed by the evidence that allergic reactions played a significant rôle in their cases. In

[4] KAHLMETER, G.: Y a-t-il des formes de rhumatisme articulaire et périarticulaire d'une nature réellement allergiques? Acta med. Skandinav., 1939, cii, 432–443.

[5] VAUGHN, W. T.: Palindromic rheumatism among allergic persons, Jr. Allergy, 1943, xiv, 256–264.

only two did allergic manifestations (urticaria) accompany an attack of arthritis, although 16 others gave a history of such reactions. Few of the cases gave a history of allergic disturbances in the family. Also they were unable to precipitate attacks by administering the suspected food or prevent them by withholding it. The pathologic tissue changes also differed from those commonly associated with allergic reactions.

There is still less support for an infectious etiology. The attacks had no relation to acute infections. Few foci of infection were found by Hench and Rosenberg in their cases, and removal of foci had no effect on the disease. Furthermore it is scarcely conceivable that a joint could undergo multiple attacks of arthritis of an infectious nature, a hundred and more, without suffering some residual injury.

The available facts obviously do not now permit a final judgment as to the cause of the disease. If the view be tentatively accepted that infection is not directly concerned, one may speculate as to some of the other mechanisms which may be operative. The rapidity with which the edema may appear and disappear, and its curiously circumscribed nature suggest that the immediate mechanism of its production is probably a localized disturbance of the circulation brought about, perhaps, through its vasomotor innervation. The analogies to the angioneurotic edema of Quincke are striking, even though the two processes differ considerably in some of their details. In many of the cases reported, other evidences of vasomotor instability have been striking. Allergic reactions undoubtedly constitute one mechanism by which such a disturbance might be precipitated. The evidence that they have been the cause in some of the cases reported is quite strong, but different causes may well be operative in other cases. Psychogenic factors, emotional disturbances of various sorts profoundly affect the vasomotor system and should receive consideration as a possible predisposing if not actual exciting cause. In fact, one of Hench and Rosenberg's cases "adopted a baby, quit worrying about herself and was cured."

The syndrome is not common, and probably does not account for more than 1 per cent of all cases of arthritis. However, several case reports have been published in the past two years. It is readily recognized, at least in its typical form, if its features are known to the observer. Diagnosis is a matter of some practical importance because of the prognosis, even though treatment thus far has been of little effect, unless perhaps in those cases in which an allergic cause has been demonstrated and eliminated.

REVIEWS

Pathology and Therapy of Rheumatic Fever. By LEOPOLD LICHTWITZ, M.D. 211 pages; 23.5 × 16 cm. Grune and Stratton, Inc., New York. 1944. Price, $4.75.

This book opens with "Rheumatic fever is a noninfectious disease." Although the etiology of rheumatic fever is still undetermined, most individuals interested in this disease believe that there is a close etiologic relationship between rheumatic fever and the hemolytic streptococcus.

Numerous statements throughout the book are open to question. The author describes "nonrheumatic chronic arthritis" in detail; the term rheumatoid arthritis does not even appear in the index although this is the accepted American and British name for this disorder.

The discussion of spondylarthritis is not in accord with our present concepts of the disease. He does not stress the importance of the early recognition of this picture when there is slight involvement of the sacroiliac joints shown by roentgenogram and only slight, if any involvement of the true small joints of the spine. In addition, it is not pointed out that rheumatoid spondylitis affects the posterior interarticular facets, the only true joints of the spine, and not the intervertebral bodies.

Differential diagnosis is dismissed in one page and a half and prognosis in somewhat under one page. Lichtwitz minimizes the importance of the recent prophylactic use of sulfanilamide in rheumatic fever in children, which, in our opinion, is of extreme importance, and should be emphasized.

It is unfortunate that the material in this book is not on a par with some of the excellent photographs. It appears that many of the statements made in the book in an authoritative manner are not in accord with the facts, as we see them in this country. We certainly do not agree with a majority of them, even though some of the concepts may have been considered in the past in continental Europe. The book is certainly not to be recommended to the general practitioner.

B. I. C.

The Avitaminoses. Second Edition. By WALTER H. EDDY, Ph.D., and GILBERT DALLDORF, M.D. 519 pages; 23.5 × 16 cm. Williams and Wilkins Co., Baltimore. 1941. Price, $4.50.

The authors have practically rewritten their earlier edition in order to incorporate the many advances made since the first publication in 1937. They have succeeded in producing a very readable text, which should be useful to anyone interested in any aspect of this wide field. An appendix includes vitamin tables and a limited number of methods.

M. A. A.

Essentials of Syphilology. By RUDOLPH H. KAMPMEIER, A.B., M.D. 518 pages; 20 × 13.5 cm. J. B. Lippincott Co., Philadelphia. 1943. Price, $5.00.

The author has written an excellent monograph on syphilology which should be of great value to the student and the general practitioner. It is simply written, and the main theme expressed is one that all teachers and lecturers in syphilis and syphilotherapy have been preaching for years, that is, no one should undertake the management of a case of syphilis without first being completely familiar with the disease, its manifestations, and its management. He has followed the treatment

routines of the Cooperative Clinical Group, with very few variations. Numerous photographs are included and are arranged in their proper places in the text. In order further to emphasize the various clinical manifestations of the disease, Dr. Kampmeier has distributed case reports throughout the text. This innovation in medical texts should prove invaluable to the student, as the symptoms, physical findings, and the results of therapy are discussed in detail in each case presented. The author has also included chapters on syphilis and marriage, educational measures in control of syphilis, social service measures, and epidemiologic factors. The entire text is well written and is very enjoyable reading.

H. M. R., Jr.,
Major, M.C., A. U. S

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Clinical Tropical Medicine. By Twenty-Seven Authors. Edited by Z. Taylor Bercovitz, M.D., Ph.D., F.A.C.P. With foreword by Wilbur A. Sawyer, M.D. 957 pages; 26.5 × 18.5 cm. 1944. Paul B. Hoeber, Inc., New York. Price, $14.00.

The Flow of Water through the Kidney. By Felix Fuchs, M.D. 67 pages; 23 × 15.5 cm. 1944. Manhattan Printing Company, New York.

Strophanthin. Clinical and Experimental Experiences of the Past 25 Years. By Bruno Kisch, M.D. 158 pages; 23.5 × 16 cm. 1944. Brooklyn Medical Press, Inc., New York. Price, $4.00.

Applied Dietetics. Second Edition. By Frances Stern. 265 pages; 26 × 18 cm. 1943. Williams and Wilkins Company, Baltimore. Price, $4.00.

Handbook of Nutrition. A Symposium Prepared under the Auspices of the Council on Foods and Nutrition of the American Medical Association. (Reprinted from the Journal of the American Medical Association with Additions.) 1943. American Medical Association, Chicago. Price, $2.50.

Safe Convoy. The Expectant Mother's Handbook. By William J. Carrington, A.B., M.D., F.A.C.S. 256 pages; 21 × 14.5 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, $2.50.

Physical Foundations of Radiology. By Otto Glasser, Ph.D., Edith H. Quimby, Sc.D., Lauriston S. Taylor, Ph.D., and J. L. Weatherwax, M.A. 426 pages; 19 × 13.5 cm. 1944. Paul B. Hoeber, Inc., New York. Price, $5.00.

Pharmacology. By Michael G. Mulinos, M.D., A.B., A.M., Ph.D. With a foreword by Charles C. Lieb, A.B., M.D. 482 pages; 22 × 14.5 cm. 1944. Oxford University Press, New York. Price, $4.00.

ERNEST E. IRONS

PRESIDENT, AMERICAN COLLEGE OF PHYSICIANS, 1944–45

DAVID P. BARR

PRESIDENT-ELECT, AMERICAN COLLEGE OF PHYSICIANS, 1944–45

Ernest E. Irons, M.D.

Ernest E. Irons, M.D., 122 S. Michigan Ave., Chicago, Ill. Born, Council Bluffs, Iowa, 1877; S.B., University of Chicago, 1900; M.D., Rush Medical College, Chicago, 1903; Ph.D., University of Chicago, 1912; Postgraduate work at University of Vienna, 1909–10; Fellow in Bacteriology, University of Chicago, 1900–01; Assistant in Bacteriology, same, 1901–03; Internship at Presbyterian Hospital, Chicago; Assistant to Dr. James B. Herrick, widely known and revered internist and Cardiologist of Chicago, 1905–12; served during World War I as Lieutenant Colonel in the Medical Corps of the U. S. Army; Member of the Council on Pharmacy and Chemistry of the American Medical Association, 1923–40; Dean, Rush Medical College, Chicago, 1923–36; Charter Member of the American Board of Internal Medicine since 1936, and Chairman of same since 1940; Rush Professor of Medicine, University of Illinois Medical School; Attending Physician, Presbyterian Hospital; Fellow of the American College of Physicians since 1929, and a member of its Board of Regents, active on its various Committees since 1938; Secretary of Board of Trustees, American Medical Association; Member of the Chicago Medical Society, Illinois State Medical Society, Association of American Physicians, American Society for Clinical Investigation, Chicago Society of Medical History, American Association of the History of Medicine, Chicago Society of Internal Medicine, Central Society for Clinical Investigation, Chicago Pathological Society, American Association of Pathologists and Bacteriologists, American Association for Study of Rheumatic Diseases, and others; author of many published papers.

David P. Barr, M.D.

Born, Ithaca, New York, August 23, 1889; A.B., 1911, Cornell University; M.D., 1914, Cornell University Medical College; LL.D., 1929, Central College (Fayette, Mo.); House Officer, 1914–16, Bellevue Hospital; Assistant Physician, 1916–17, and Research Fellow, 1919–22, Russell Sage Institute; First Lieutenant, 1917–19, Medical Reserve Corps, American Expeditionary Forces; Adjunct Assistant Visiting Physician, 1919–22, and Assistant Physician, 1922–24, Bellevue Hospital; Instructor in Medicine, 1916–22, and Assistant Professor of Medicine, 1922–24, Cornell University Medical College; Physician-in-Chief, 1924–41, Barnes Hospital, St. Louis; Busch Professor of Medicine, 1924–41, Washington University Medical College, St. Louis; Physician-in-Chief, 1941 to date, New York Hospital; Professor of Medicine, 1941 to date, Cornell University Medical College; Honorary Consulting Physician, 1942 to date, Bellevue Hospital; Fellow, and member of the Council on Pharmacy and Chemistry, American Medical Association; Fellow (1927), and member of the Board of Regents for many years, American College of Physicians; President, 1938–39, Association for the Study of Internal Secretions; Diplomate and member, American Board of Internal Medicine; New York State and County Medical Societies; American Society for Clinical Investigation; Central Society for Clinical Research; Association of American Physicians; New York Academy of Medicine; Harvey Society; Practitioners Society of New York; New York Medical and Surgical Society; Committee on Gas Casualties, National Research Council; Committee, War-Time Graduate Medical Meetings; Sigmu Nu and Alpha Omega Alpha Fraternities; author of many published papers and editor of "Modern Medical Therapy in General Practice."

COLLEGE NEWS NOTES

WAR SESSION AND ANNUAL BUSINESS MEETING OF THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians held at Chicago on March 31–April 1, 1944, the annual meetings of its various Committees, a Scientific War Session, a combined Executive Meeting of its Board of Regents and Board of Governors, and its Annual Business Meeting for the receipt of reports from the Executive Secretary, the Secretary General and the Treasurer, and for the election of Officers, Regents and Governors.

The program of the War Session was as follows:

Presiding Officer, JAMES E. PAULLIN, F.A.C.P., President, Atlanta, Ga.

1. "Aerial Transportation of the Sick and Wounded." DAVID N. W. GRANT, F.A.C.S., Major General, (MC), U. S. Army, The Air Surgeon, Army Air Forces, Washington, D. C. (Paper read by W. PAUL HOLBROOK, F.A.C.P., Colonel, (MC), U. S. Army, Washington, D. C.)

ARMY PROGRAM

Opening Remarks. HUGH J. MORGAN, F.A.C.P., Brigadier General, (MC), U. S. Army, Professional Service Division, Office of the Surgeon General, Washington, D. C.

2. "Experiences in India." THOMAS FITZ-HUGH, JR., F.A.C.P., Lieutenant Colonel, (MC), U. S. Army, McGuire General Hospital, Richmond, Va.

3. An informal paper on the treatment of tropical diseases in soldiers evacuated from overseas. ALEXANDER MARBLE, F.A.C.P., Colonel, (MC), U. S. Army, Harmon General Hospital, Longview, Tex.

NAVY PROGRAM

4. "The Great Need for Internists in the Navy Medical Program." Ross T. McINTIRE, F.A.C.P., Vice Admiral, (MC), U. S. Navy, The Surgeon General, Washington, D. C. (Paper read by LUTHER SHELDON, JR., Rear Admiral, (MC), U. S. Navy.)

5. "Medical Men in the Solomons." DON S. KNOWLTON, F.A.C.S., Captain, (MC), U.S.N.R., Camp Surgeon, Camp Lejeune, New River, N. C. (Action in South Pacific with First Marine Division.)

6. "Medical Lessons Learned from the Evacuation of Casualties." ALBERT M. SNELL, F.A.C.P., Captain, (MC), U.S.N.R., Rochester, Minn.

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7. "Scrub Typhus in New Guinea." FRANCIS G. BLAKE, F.A.C.P., Director, Committee on Epidemiological Survey, New Haven, Conn.

At the Annual Business Meeting, Dr. Ernest E. Irons, Chicago, was inducted to office as President of the College and Dr. David P. Barr, New York City, was elected President-Elect. Dr. Charles H. Cocke, Asheville, N. C., was re-elected First Vice President; Dr. Walter W. Palmer, New York City, was elected Second Vice President; and Dr. James J. Waring, Denver, Colo., was elected Third Vice President.

The retiring President, Dr. James E. Paullin, was elected a Regent of the College. Lieutenant Colonel William S. Middleton, (MC), AUS, formerly of Madison, Wis., now serving as Consultant in Medicine in the European area, Colonel Walter B. Martin, (MC), AUS, formerly of Norfolk, Va., Dr. George F. Strong of Vancouver, B. C., and Dr. LeRoy H. Sloan of Chicago were elected Regents. The list of Governors of the College appears on the inside back cover of this journal.

On Saturday evening, April 1, in the Red Lacquer Room of the Palmer House, Chicago, Dr. James E. Paullin delivered the presidential address, dealing with the activities of the College during his two years of office, and Dr. Ernest E. Irons delivered his inaugural address entitled, "American Medicine in War and Peace." Both of these addresses will be published in an early issue of the ANNALS, as will also many of the addresses on the Scientific Session and the Minutes of the various Executive Sessions. The meeting was attended by nearly every Regent and Governor of the College, or their alternates, and by a large and representative group of Fellows, Associates and guests.

ADDITIONAL A.C.P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,622 Fellows and Associates of the College on active military duty. Herewith are reported the names of 15 additional members, bringing the grand total to 1,637.

Benjamin B. Blum
John K. Deegan
Grant O. Favorite
David Fertig
Mark W. Garry
Reid R. Heffner
Raymond Luft
Leo J. Meienberg
Kenneth E. Quickel
John P. Rattigan
Norman S. Skinner
Stanley R. Szymansi
Harry Warshawsky
Ellis W. Willhelmy
Solomon L. Zimmerman

The following members of the American College of Physicians have been honorably discharged from active service in the armed forces:

Dr. George Baehr (U. S. Public Health Service-Civilian Defense)—discharged 2/29/44.

Lieutenant Harry Parks, (MC), AUS, Atlanta, Ga.—discharged 12/19/43.

Lieutenant Theodore R. Van Dellen, (MC), AUS, Chicago, Ill.

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows, listed in the order of subscription, have become Life Members of the College:

Dr. John T. Sample, Saginaw, Mich.
Dr. Joseph T. Martin, Oklahoma City, Okla.
Dr. Mason I. Lowance, Atlanta, Ga.
Dr. David A. Cooper, Philadelphia, Pa.
Dr. Merle M. Miller, Philadelphia, Pa.
Dr. Constantine F. Kemper, Denver, Colo.
Dr. Abel A. Applebaum, Toledo, Ohio

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Reprints

J. Edward Berk, F.A.C.P., Captain, (MC), AUS—1 reprint;
Joseph H. Delaney, Associate, Captain, (MC), AUS—1 reprint;
Dr. C. Wesley Eisele, F.A.C.P., Chicago, Ill.—7 reprints;
Dr. Robert H. Felix, F.A.C.P., U.S.P.H.S.—1 reprint;
Ellis H. Hudson, F.A.C.P., Commander, (MC), USNR—1 reprint;
Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio—7 reprints;
Dr. Richard E. D. Kepner, F.A.C.P., Honolulu, T. H.—2 reprints;
Jack D. Kirshbaum, Associate, Lieutenant Colonel, (MC), AUS—1 reprint;
Perry J. Melnick, F.A.C.P., Major, (MC), AUS—1 reprint;
Dr. M. Hill Metz, F.A.C.P., Dallas, Tex.—3 reprints;
Dr. William H. Ordway, F.A.C.P., Mount McGregor, N. Y.—1 reprint;
J. Shirley Sweeney, F.A.C.P., Lieutenant Colonel, (MC), AUS—1 reprint.

Also among publications received was a copy of the Banting Memorial Lecture, "The Social Implications of Scientific Research," delivered before the Faculty of Medicine of the University of Toronto, February 21, 1944, by Dr. John R. Williams, F.A.C.P., Rochester, N. Y.

A. C. P. Regional Meeting, Los Angeles

A Regional Meeting of the members of the American College of Physicians of Southern California was held at Los Angeles, February 26, 1944, under the Chairmanship of Dr. Roy E. Thomas, Governor for that district. The meeting was held in the form of a social evening and dinner at the California Club, and was addressed by Dr. William Dock, recently appointed Professor of Medicine at the University of Southern California; subject, "The Predilection of Atherosclerosis for the Coronary Arteries." Eighty-four Fellows and Associates were in attendance and the meeting was reported to be eminently successful.

A. C. P. Postgraduate Courses

The following schedule of short refresher courses sponsored by the College are now in session or about to start:

Course No. 1. Special Phases of Internal Medicine, University of Michigan, Medical School, Ann Arbor, Mich., Dr. Cyrus C. Sturgis, F.A.C.P., Director.

Course No. 2. Clinical Medicine—Hematology, Ohio State University College of Medicine, Columbus, Ohio, Dr. Charles A. Doan, F.A.C.P., Director.

Course No 3. Internal Medicine (Selected Phases), Massachusetts General Hospital, Boston, Mass., Dr. James H. Means, F.A.C.P., Director.

This activity of the College has proved extremely popular in the past, but never more so than for the current courses. Each course was greatly oversubscribed by members of the College and very few non-members could be accommodated.

The Committee on Post-War Planning for Medical Service

A meeting of the combined Committees of the American College of Physicians, American College of Surgeons and American Medical Association was held in Washington, March 4, 1944.

At this meeting important matters under consideration were:

1. A report on a questionnaire which has been sent to a sample of 3,000 medical officers, distributed equally among Army, Navy and Public Health groups. Some

of the replies had already been returned and analyzed. It was apparent that very few physicians after discharge from active duty will be interested in internships, but that there will be a large number who will want further training, such as they would receive in resident positions or as assistants in a clinic. Certain modifications in the questionnaire were discussed and it was indicated that an attempt would be made to distribute the new questionnaire to as large a proportion of medical officers as permissible.

2. A consideration of resolutions adopted by the Council on Medical Education and Hospitals by the American Medical Association to the effect that the whole of the post-war program of the distribution of medical care should be considered as a unit for which a central agency should be established under the auspices of the American Medical Association but composed of representatives of interested groups, such as the American College of Physicians, American College of Surgeons, the American Hospital Association, the Association of American Medical Colleges, the Advisory Board for Medical Specialties, and the Procurement and Assignment Service for Physicians. Such a coördinated group could give unified direction and economy of administrative effort to the various subdivisions into which the whole problem will naturally fall. These include (*a*) intern education, (*b*) allocation of doctors to communities in need of their services, (*c*) adjustment of requirements of the specialty boards to physicians whose careers have been interfered with by the war, and other issues that may arise from the war.

The Council signified its willingness to accept its assignment of the problems of internships and residencies after the war, as well as other aspects that come within its province.

The Committee voted to ask representatives be appointed from the Federation of State Licensing Boards, the Association of American Medical Colleges and the American Hospital Association. Already the American College of Physicians, the American College of Surgeons, the Advisory Boards for Medical Specialties and the Procurement and Assignment Service have representatives on the Committee.

The Chairman of the Central Committee on Post-War Planning for Medical Service, Dr. Roger I. Lee, was authorized to appear in person or by designated representatives at any hearing on bills affecting medical practice and medical education, both for the present and for the period after the war.

Dr. Walter W. Palmer, New York City, is Chairman of the group representing the American College of Physicians.

WAR-TIME GRADUATE MEDICAL MEETINGS

Future Schedule

REGION No. 1 (Maine, New Hampshire, Vermont, Massachusetts)—Dr. C. S. Keefer, Chairman; Dr. M. C. Sosman, Dr. A. W. Allen

REGION No. 2 (Connecticut, Rhode Island)—Dr. S. B. Weld, Chairman; Dr. C. Barker, Dr. A. M. Burgess

Dispensary, U. S. Naval Air Station, Brunswick, Maine

April 20 Acute Abdominal Emergencies

Station Hospital, Fort Williams, Portland, Maine

April 20 Blood Dyscrasias and Transfusions

Station Hospital, Presque Isle, Maine

April 20 Peripheral Vascular Disease

Dispensary, U. S. Naval Construction Training Center, Quoddy Village, Maine

April 20 Joint Injuries

Station Hospital, Grenier Field, Manchester, New Hampshire

April 19 Chest and Abdominal Injuries

U. S. Naval Hospital, Portsmouth, New Hampshire

April 20 Head, Spine and Nerve Injuries

Station Hospital, Fort Banks, Boston, Massachusetts

April 20 Pilonidal Sinus and Common Diseases of the Anus and Rectum

U. S. Naval Hospital, Chelsea, Massachusetts

April 20 Burns and Reconstruction Surgery

Lovell General Hospital, Fort Devens, Massachusetts

April 20 Acute Infections of the Central Nervous System

Station Hospital, Camp Edwards, Massachusetts

April 20 The Use of Penicillin and the Sulfa Drugs

Cushing General Hospital, Framingham, Massachusetts

April 20 The Psychoneuroses and Their Management

Station Hospital, Camp Myles Standish, Taunton, Massachusetts

April 20 Stomach, Biliary Tract, Intestinal Disorders

U. S. Marine Hospital, Brighton, Massachusetts

April 20 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation

Station Hospital, Westover Field, Chicopee Falls, Massachusetts

April 20 Contagious Diseases and Complications

Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island

April 20 The Pneumonias and Other Respiratory Infections

U. S. Naval Hospital, Newport, Rhode Island

April 20 Symposium on Physiotherapy

Air Corps Station Hospital, New Haven, Connecticut

April 20 Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases

Station Hospital, Fort H. G. Wright, Fishers Island, New York

April 20 Diarrheal Diseases

The names of the speakers who will participate in the above programs are to be announced.

REGION No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Joliffe, Dr. H. W. Cave

Halloran General Hospital, Staten Island, New York

May 9	Cardiac Pain	Dr. John J. H. Keating

Grand Central Palace, 480 Lexington Avenue, New York City, New York

April 21	General Surgical Approach to the Abdomen	Dr. John F. Erdmann
April 28	Disorders of the Low Back (to be repeated on May 5)	Dr. Arthur Krida
May 12	Neuropsychiatric Problems in the Army (to be repeated on May 19)	Colonel Douglas T. Thom

Camp Shanks, Orangeburg, New York

April 20	Anesthesia	Dr. Emery A. Rovenstine
April 27	Neuropsychiatric Problems in the Army	Colonel William C. Porter

Station Hospital, Fort Niagara, New York

April 19	Head Injuries
April 26	Pulmonary Tuberculosis
May 3	Chest Injuries

The speakers' names for these programs will be announced.

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Lieutenant Commander G. C. Griffith, Chairman; Dr. J. S. Rodman, Dr. B. P. Widmann

Station Hospital, Camp Kilmer, New Jersey

April 24	Psychosomatic Aspects of Hypertension	Dr. Edward Weiss
May 8	Rickettsia Infections	Dr. William Sawitz

Fort Monmouth, New Jersey

April 19	Fundamentals of Anesthesia	Dr. Frederick P. Haugen
April 26	Peripheral Nerve Block	Lieutenant Commander Don Hale
May 3	Diagnosis and Treatment of the Neuropsychiatric Patient in a Naval Hospital	Commander T. N. Spessard
May 10	Head Injuries: Their Diagnosis and Treatment	Dr. Temple Fay

Indiantown Gap, Pennsylvania

April 19	Viral Pneumonia	Dr. Truman Schnabel
April 26	Yellow Fever	Dr. William Sawitz
May 3	Head Injuries: Their Diagnosis and Treatment	Dr. Temple Fay
May 10	Acute Glomerulonephritis (Trench Nephritis)	Dr. George Morris Piersol

England General Hospital, Atlantic City, New Jersey

May 2	Malaria	Dr. W. Harding Kneedler and Dr. William Sawitz
May 16	Leishmaniasis	Dr. Julia Morgan and Dr. William Sawitz

Naval Hospital, Philadelphia, Pennsylvania

April 28	Rickettsia Infections	Dr. William Sawitz
May 12	Management of Pneumonia	Dr. Harrison P. Flippin

On Tuesday, April 18, there will be a meeting under the combined auspices of the Newcastle County Medical Society of Delaware and the War-Time Graduate Medical Meetings at the Delaware Academy of Medicine in Wilmington. Dr. Henry J. Tumen will address the group on the subject of Acute Infectious Hepatitis.

REGION No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. G. L. Weller

Fort Eustis, Virginia

April 27 (tentative)	Psychosomatic Medicine	Dr. Louis A. Schwartz
May 11	Psychoneurosis Among the Armed Forces	Dr. Claude L. Neale

Camp Lee, Virginia

April 21 (tentative)	Plastic and Maxillo-facial Surgery	Dr. Guy Harrison
April 28	Respiratory Diseases and Their Treatment by Chemotherapeutic Agents	Captain Paul S. Strong
May 5 (tentative)	Rheumatism	Lieutenant Joseph L. Hollander
May 12 (tentative)	Prevention and Treatment of Wound Infections with Sulfonamides	Lieutenant Colonel Okla W. Sicks

Camp Pickett, Virginia

April 19 (tentative)	Traumatic Surgery of the Abdomen	Lieutenant Colonel W. R. Galbreath
April 21	War Wounds of the Genito-Urinary Tract	Major William Bisher

Langley Field, Virginia

April 18	Treatment of Trauma to the Chest	Major Leonard Bush
April 25	Aviation Medicine, General	Dr. Ludwig Lederer
May 2 (tentative)	Anesthesia—Selection and Contra-indications	Captain Allen Widome
May 9 (tentative)	Psychosomatic Medicine	Lieutenant Sidney U. Wenger

Fort George G. Meade, Maryland

April 21	Aviation Medicine with Special Reference to the Cardiovascular System	Dr. Walter A. Bloedorn
April 28	The Use of Sulphamerazine in Dysentery	Dr. Lay Martin
May 4 (tentative)	Gastric and Duodenal Ulcers	Dr. William McC. Ballinger
May 12 (tentative)	Narcosynthesis and Hypnotism	Dr. Winfred Overholser

Norfolk Naval Hospital, Portsmouth, Virginia

April 26 (tentative)	Peripheral Nerve Injuries	Dr. Claude C. Coleman
May 11 (tentative)	Psychosomatic Medicine	Captain Charles A. Spangler

Fort Belvoir, Virginia

April 17 (tentative)	Diagnosis and Treatment of Shock	Lieutenant Colonel D. B. Kendrick, Jr.
April 24 (tentative)	New Chemotherapeutic Agents and Their Uses in Practice	Dr. Harry F. Dowling

Newton D. Baker General Hospital, Martinsburg, West Virginia

April 17 (tentative)	Malaria	Dr. Walter A. Baetjer
April 24	Virus and Bacterial Pneumonias and Their Treatment	Dr. Warfield T. Longcope
May 1 (tentative)	Crushing Injuries of the Extremities	Dr. Floyd Shaffer
May 8 (tentative)	Physiotherapy in War Wounded	Lieutenant Commander Harry Etter
May 15 (tentative)	Psychosomatic Medicine	Dr. Jacob H. Conn

Dr. Albert Soiland, F.A.C.P., Los Angeles, is on active duty at the U. S. Naval Hospital, Long Beach, California. He has been in the Naval Reserve for 30 years and has represented the Navy Medical Department in most of the foreign countries of Europe and South America. It is said that Dr. Soiland is the oldest Captain on active duty in the Medical Corps of the Navy, aged 70.

Dr. Wallace M. Yater, F.A.C.P., Washington, D.C., has been appointed the official representative of the American College of Physicians in the Division of Medical Sciences of the National Research Council, to succeed Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, whose term of three years will expire June 30, 1944.

Captain Richard A. Kern, F.A.C.P., (MC), USNR, has returned to Philadelphia from overseas duty and has been assigned as Chief of Medicine at the U. S. Naval Hospital there.

Dr. Leon Collins, F.A.C.P., of Philadelphia, was recently advanced to Lieutenant Colonel, (MC), AUS, and at last report was on duty at the Station Dispensary, Stinson Field, San Antonio, Texas.

Lt. Col. Irving S. Wright, F.A.C.P., (MC), AUS, formerly of New York City, has been made the Medical Consultant to the Sixth Service Command with Headquarters in Chicago.

Dr. George H. Baehr of New York City, who has served as Chief Medical Officer of the Office of Civilian Defense at Washington, almost since the outbreak

of the War, has returned to civilian status as of March 1, 1944, and his office is located at One East 100th Street, New York City.

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, addressed the Jackson County "Health Forum," Kansas City, Mo., March 15 on "Arthritis and Related Diseases."

Dr. Howard Wakefield, F.A.C.P., and Dr. Selim W. McArthur, Chicago, Ill., presented a paper on "Observations on the Human Electrocardiogram Made during Experimental Distention of the Gall-Bladder," before the Chicago Society of Internal Medicine, February 28.

Dr. Franklin G. Ebaugh, F.A.C.P., Professor of Psychiatry at the University of Colorado School of Medicine, Director of the Colorado Psychopathic Hospital, at present a Colonel in the Medical Corps of the United States Army and Chief Consultant in Psychiatry for the Eighth Service Command, Dallas, Texas, was recently elected President of the Association for Research in Nervous and Mental Diseases.

Fourteenth Annual Conference, Oklahoma City Clinical Society

The Oklahoma City Clinical Society will hold its Fourteenth Annual Conference with headquarters in the Biltmore Hotel, Oklahoma City, October 23–26, 1944.

New York Academy of Medicine, Graduate Fortnight

The Annual Graduate Fortnight of the New York Academy of Medicine will be held October 9–20, 1944, on the subject, "Infections and Their Treatment." Special emphasis will be placed upon the more recent chemotherapeutic agents.

The Fortnight will include Morning Panel Discussions, Afternoon Hospital Clinics, Evening Lectures and Pathological Demonstrations. There will be a scientific exhibit, including the more recent pharmaceuticals and an appropriate Library exhibit. Programs may be obtained by addressing the Academy at 2 East 103rd Street, New York City 29.

Dr. James S. Sweeney, F.A.C.P., (MC), AUS, formerly of Dallas, Texas, was recently promoted to the rank of full Colonel.

Dr. Samuel Blinder, F.A.C.P., New York City, was recently appointed Associate Clinical Professor of Medicine at the New York Medical College.

New Site for Medical College, University of Alabama

A commission, authorized by the 1943 Legislature of the State of Alabama, has selected Birmingham as the site for the four-year Medical College of the University of Alabama. A full city block, adjacent to Jefferson and Hillman Hospitals, will be furnished by Jefferson County. $1,000,000.00 for construction of the building and $366,750.00 annually for maintenance and scholarships have been appropriated by the Legislature.

The Medical Society of Virginia will hold its next annual meeting October 23–25, 1944.

Dr. William B. Porter, F.A.C.P., Professor of Medicine at the Medical College of Virginia, recently addressed the (Raleigh, N. C.) Academy of Medicine on the Cardio-Diaphragmatic Syndrome.

Dr. Walter L. Palmer, F.A.C.P., Chicago, addressed a Forum on Cancer of the Stomach under the auspices of the Chicago Cancer Committee, February 21, on "Diagnosis and Symptoms."

Dr. Alfred Meyer, F.A.C.P., oldest living graduate of the house staff of Mt. Sinai Hospital, New York City, was honored at a special ceremony at that institution recently. Dr. Meyer will observe his 90th birthday this year.

Dr. Hugh S. Cumming, F.A.C.P., Washington, D. C., Director of the Pan-American Sanitary Bureau and formerly Surgeon General of the U. S. Public Health Service, was the recipient of the William Freeman Snow Medal for "outstanding service in the field of social hygiene," presented February 1 during the annual dinner meeting of the American Social Hygiene Association. The Medal was presented by Dr. Merrittee W. Ireland, F.A.C.P., former Surgeon General of the U. S. Army.

Dr. Louis Hamman, F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, delivered the Roger S. Morris Memorial Lecture, March 7, at the University of Cincinnati College of Medicine; his subject, "The Diagnostic Implications of Aortic Insufficiency."

The Canadian Medical Association will hold its 75th Annual Meeting in Toronto, May 22–26, 1944.

Dr. Tinsley R. Harrison, F.A.C.P., heretofore Professor of Medicine at the Bowman Gray School of Medicine, Winston-Salem, N. C., has been appointed Dean of Southwestern Medical College, Dallas, Texas, to take office immediately. He will also serve as Executive Professor of Experimental Medicine and Professor of Medicine.

Dr. Carl J. Wiggers, F.A.C.P., Professor and head of the Department of Physiology, Western Reserve University School of Medicine, Cleveland, addressed the Chicago Heart Association February 29 on, "Some Cardiovascular Aspects of Shock and Transfusion."

Dr. Arthur W. Grace, F.A.C.P., Professor of Clinical Dermatology and Syphilology, Long Island College of Medicine, Brooklyn, has been conducting a course in Tropical Diseases in Newark, N. J., under the auspices of the State Department of Health.

Dr. N. Stanley Lincoln, F.A.C.P., for the past eight years Superintendent of Mount Morris Tuberculosis Hospital, Mount Morris, N. Y., has transferred to a similar position at the Hermann M. Biggs Memorial Hospital, Ithaca, to succeed Dr. John K. Deegan, F.A.C.P., who has entered military service.

Dr. Paul Brindley (Associate) Galveston, was recently elected President-Elect of the Texas Society of Pathologists. Dr. May Owen, F.A.C.P., and Dr. John J. Andujar, F.A.C.P., Forth Worth, have been elected Vice-President and Secretary-Treasurer, respectively.

Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., Secretary of the American Gastroenterological Association, has announced the annual meeting of that society at the Drake Hotel, Chicago, June 12–13, 1944.

Squibb Award Announced

The 1944 E. R. Squibb & Sons Award, $1,000.00 is available to an investigator in the United States or Canada "for an outstanding contribution in endocrinology." Nominations should be sent to the Secretary of the Association for the Study of Internal Secretions, Dr. Henry H. Turner, F.A.C.P., 1200 North Walker Street, Oklahoma City, Okla.

Harold J. Harris, M.D., F.A.C.P., Lt. Comdr., (MC), USNR, addressed the Society of Medical Jurisprudence on February 14 on the subject of brucellosis, especially from its medico-legal aspects. Discussion was opened by Dr. Frank A. Calderone, Deputy Commissioner of Health of New York City.

Major William F. Confair, F.A.C.P., Benton, Pa., was honorably discharged from the Army October 25, 1943. His active duty began December 26, 1940. He became a casualty in the Aleutian Islands, was returned to the United States, treated at the Walter Reed General Hospital and subsequently discharged due to physical disqualification.

Rear Admiral Ross T. McIntire, F.A.C.P., Surgeon General of the United States Navy, has been advanced to Vice Admiral.

SPECIAL NOTICES

The 1944 Graduate Fortnight

The annual Graduate Fortnight of The New York Academy of Medicine will take place October 9 to 20, on the subject, "Infections and Their Treatment." Special emphasis will be placed upon the more recent chemotherapeutic agents.

The Fortnight, as in the past, will include Morning Panel Discussions, Afternoon Hospital Clinics, Evening Lectures and Pathological Demonstrations. There will also be a scientific exhibit, including the more recent pharmaceuticals and an appropriate Library exhibit.

For information and registration, address the Secretary, Committee on Medical Education of The New York Academy of Medicine, 2 East 103 Street, New York City 29, New York.

Two annual awards have been established under the sponsorship of the American Academy of Allergy effective January 1, 1944. The first is the Abbott Award, an annual prize of $200.00 established by the Abbott Laboratories of Chicago, Ill., to be granted annually for the most important advancement in the field of allergy, or for the development of a research problem on any phase of this subject. For this award will be considered both Members and non-Members of the Academy.

The Secretary's Prize, the second of the awards, is a medal to be given annually to a member of the Academy for the most outstanding achievement of the year in the general field of allergy.

The annual exhibition of the American Physicians' Art Association will be held with the A.M.A. Session, June 12 to 16, 1944 in the gallery of the beautiful Grand Ballroom, Stevens Hotel, Chicago.

Physicians who follow an artistic hobby such as sketching, photographing, water coloring and painting are invited to submit samples of their work for exhibition. Prizes will be awarded.

Full particulars may be obtained by writing to the Secretary, Dr. F. H. Redewill, Flood Bldg., San Francisco, Calif.

The second national Conference on Convalescence and Rehabilitation will be held on April 25 and 26 at The New York Academy of Medicine, under the auspices of the Committee on Public Health Relations of the Academy and with the financial support of the Josiah Macy, Jr. Foundation. Ranking medical officers of the Army, Navy, Army Air Forces, and U. S. Public Health Service, and the Veterans Administration will present the projects in this field which have been developed in their respective services. In addition, discussion will be focused on such fundamental topics as nutrition, motivation, retraining, research, and the rôle of home, hospital, and industry. Admission will be by invitation. Dr. Oswald R. Jones is the chairman of the committee on arrangements and Dr. E. H. L. Corwin, 2 East 103rd Street, the executive secretary.

OBITUARIES

DR. ALBERT EDWIN LARKIN

Dr. Albert Edwin Larkin was born in Camillus, New York, in 1871; Ph.B. 1894, Colgate University; M.D., 1897, Syracuse University College of Medicine; interned St. Joseph Hospital, 1897–1898. He did postgraduate study in Berlin and Vienna, 1898–1899; additional postgraduate work later at Johns Hopkins University School of Medicine and Harvard Medical School. He was Assistant Visiting Physician, St. Joseph Hospital, for many years; Associate Professor of Clinical Medicine, 1908–1911, Professor of Clinical Medicine, 1911–1933, and since 1933, Professor Emeritus of Clinical Medicine, Syracuse University College of Medicine; President Board of Public Education, 1912–1915; for many years on the Staff of the Syracuse Memorial Hospital; member of the Board of Trustees of the Syracuse University, 1921–1933; Diplomate, American Board of Internal Medicine; former Treasurer, former Vice President and former President, Syracuse Academy of Medicine; member of the Onondaga County Medical Society, Medical Society of the State of New York; Fellow, American Medical Association and Fellow of the American College of Physicians since 1920; member of the Onondaga Golf and Country Club; member of the Thursday Night Club and Hiawatha Club (both local Medical Societies); member of Alpha Omega Alpha; Attending Physician at the Onondaga County Hospital for the past two years. His special interest in medicine was cardiology.

Dr. Larkin died November 2, 1943, of generalized arteriosclerosis and macrocytic anemia; aged 72.

He had many friends among the profession and the laity, by whom he is greatly missed.

NELSON G. RUSSELL, SR., M.D., F.A.C.P.,
Governor for Western New York

CAPTAIN HARRY D. MILLER

Captain Harry D. Miller (Associate), born in Indianapolis, Ind., September 29, 1908, and previous to the War located at Shelbyville, Ind., was killed in action February 2, 1944, in Algeria, according to word received by his widow, Mrs. Margaret Miller. A skull fracture was the cause of his death, though no details have yet been received.

Dr. Miller held the degrees of B.S. from the University of Illinois and M.D. (1933) from the University of Illinois College of Medicine. He did postgraduate work at the Cook County Postgraduate School of Medicine. He took over the practice of the late Dr. Bayard Keeney, a Fellow of this College, Shelbyville. He displayed a keen interest in the field of Internal Medicine, being especially interested in Allergy.

In the short time he had been in Shelbyville, Dr. Miller was well received

by the profession and by the lay public, and his previous training in postgraduate work made him one of the promising internists of the State.

His death at such an early period of life is recorded with deep regret.

ROBERT M. MOORE, M.D., F.A.C.P.,
Governor for Indiana

DR. CHARLES W. BURR

Dr. Charles W. Burr, F.A.C.P., Philadelphia, distinguished physician and citizen, died on February 19, 1944.

Dr. Burr was born in Philadelphia in 1861, and received his elementary and university education in Philadelphia schools. The degree of Doctor of Medicine was conferred upon Dr. Burr by the University of Pennsylvania in 1886 following which he engaged in postgraduate study at the Universities of Berlin and Vienna.

For many years, Dr. Burr was associated with the late Dr. S. Weir Mitchell. From 1896 to 1931, he was neurologist at the Philadelphia General Hospital, and since 1931, he had been psychiatrist at that hospital. From 1901 to 1931, Dr. Burr was Professor of Mental Diseases at the University of Pennsylvania, and in 1931 he became Professor Emeritus.

For outstanding service in his chosen field, Dr. Burr was awarded many honorary awards. Among these were the honorary degree of Doctor of Science from the University of Pennsylvania in 1933, and from the same institution, the alumni award of merit in 1936.

Dr. Burr faithfully served organized medicine during his long and active career. During different periods of his lifetime, he served as president of the American Neurological Association, the Philadelphia Psychiatric Society, which he likewise founded, the Philadelphia Neurological Society, the Pathological Society of Philadelphia and the Philadelphia Medical Club.

He was a member of the Philadelphia County Medical Society, the Pennsylvania State Medical Association, the American Medical Association, and a Fellow of the College of Physicians of Philadelphia.

Dr. Burr made numerous contributions to the field of medicine. His active and keen mind stimulated others to outstanding achievement, and his passing from this world is sadly acknowledged by all his friends and associates, and in particular the membership of the American College of Physicians, in which group he has held a distinguished position since 1926.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania